Metal-based asymmetric catalysis in Baeyer-Villiger oxidations

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C. Bolm, O. Beckmann, A. Cosp, C. Palazzi, *Synlett* **2001**, *9*, 1461.

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1 Introduction

1.1 General introduction

"In the field of observation, chance favours only the prepared mind"

Louis Pasteur

It was the year 1848 when Pasteur began to study a salt of racemic acid, a substance deposited on the wine casks during fermentation (the name racemic derived from the Latin, *racemus*, a bunch of grapes). It was known at that time that certain natural substances such as quartz crystals, turpentine and solution of sugars could also twist polarized light, but no one understood how that occurred. It was, however, left to the genious of Pasteur to extend this correlation from the realm of crystals to the realm of molecules. The French scientist had succeeded in separating crystals of the sodium ammonium salt of (+)- and (−)-tartaric acid from the racemic (nonrotating) mixture. When the salts of the mixed racemic acid, which was found in wine caskets, was recrystallized by slow evaporation of its aqueous solution, large crystals formed which, by means of a pair of tweezers and a lens, were separated by Pasteur in two groups. When he then separately redissolved the two kinds of crystals, he found that one solution polarized light to the right, whereas the other rotated to the left. Although Pasteurs´s observation of the different shape of crystals, his separation of them and his deduction about the meaning of their opposite effects on polarized light were indeed acts of genius, serendipity played a large part in his discoveries: the sodium ammonium salt of racemic acid is the only one that crystallizes this way and that can be separated mechanically; in addition the crystallization in two forms occurs only at a temperature below 26 °C. Nevertheless, his pionieering work on the resolution of racemic acid led the way for other chemists to explain the relationship of chirality in molecular structure to biological activity.[1]

Although it is not fundamental to know that left-handed molecules of racemic acid rotate the plane of polarized light counterclockwise, it is tremendously important to understand why a right-handed molecule of vitamin C, (+)-ascorbic acid, is a vitamin, whereas (−)-ascorbic acid has no biological activity; why (−)-chloromicetin is a potent antibiotic and the enantiomer is

[1] *The Fundation of Stereochemistry*, (Ed. G. M. Richardson), American Book Co., New York, **1901**.

not; why (−)-adrenalin is many times more active as a hormone than the (+)-adrenalin. Chirality is of prime significance, as most of the biological macromolecules of living systems occur in nature in one enantiomer form only. A biologically active chiral compound interacts with its receptor site in a chiral manner and enantiomers may be discriminated by the receptor in very different ways. Biological systems, in most cases, recognize the members of a pair of enantiomers as different substances, and the two enantiomers will elicit different response.[2] Thus, one enantiomer may act as a very effective therapeutic drug whereas the other enantiomer is highly toxic. There are several methods to obtain enantiomerically pure materials, which include classical optical resolution via diastereomers,[3] chromatographic separation of enantiomers,[4] enzymatic resolution,[5] chemical kinetic resolution[6] and asymmetric synthesis. [7] Among the type of asymmetric reactions, the most desirable and the most challenging is catalytic asymmetric synthesis, since one chiral catalyst molecule can create millions of chiral product molecules, just as enzymes do in biological systems. Among the significant achievements in basic research, asymmetric hydrogenation of dehydroaminoacids, as described by Knowles et al.,[8] the Sharpless epoxidation,[9] and the hydrogenation process developed by Noyori,[10] deserve particular attention because of the tremendous impact these processes have had in synthetic organic chemistry. Several asymmetric catalytic processes have found application in industry,[11] as for instance the Takasago process (asymmetric isomerization), the Sumitomo process (asymmetric cyclopropanation), the Arco process (Sharpless epoxidation) and of course the Monsanto process (asymmetric hydrogenation). It is to researchers in this field the 2002 Nobel Price in Chemistry has been awarded; the laureates have developed catalysts for two important classes of reactions in organic chemistry: hydrogenations and oxidations. William S. Knowles, Ryoji Noyori and K. Barry Sharpless shared the price in 2002.

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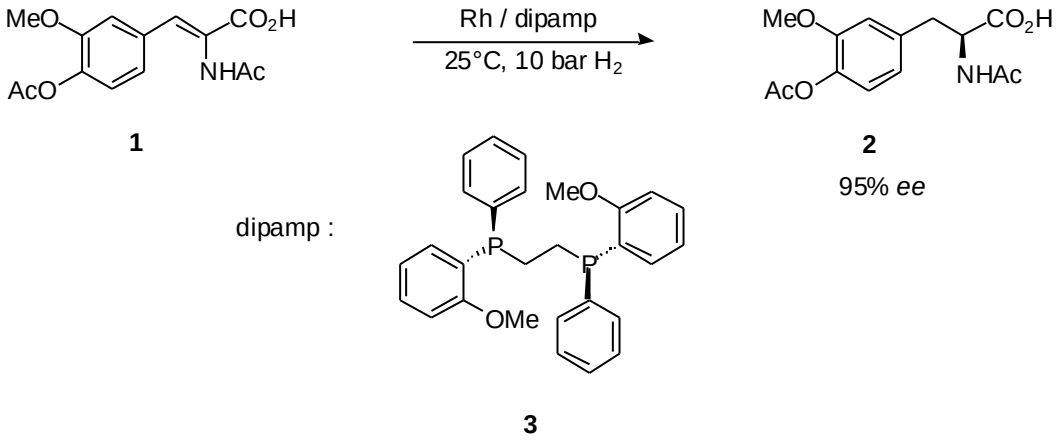
[2] W. H. DeCamp, *Chirality* **1989**, *1*, 2.
[3] T. Vries, H. Wynberg, E. van Echten, J. Koek, W. ten Hoeve, R. M. Kellog, Q. B. Broxterman, A. Minnaard, B. Kaptein, S. van der Sluis, L. Hulshof, J. Kooistra, *Angew. Chem.* **1998**, *110*, 2491; *Angew. Chem. Int. Ed.* **1998**, *37*, 2349.
[4] *A Practical Approach to Chiral Separations by Liquid Chromatography* (Ed.: G. Subramanian), VCH, Weinheim, **1994.**
[5] *Enzyme Catalysis in Organic Synthesis* (Eds.: K. Drauz, H. Waldmann), VCH, Weinheim,**1995**.
[6] a) H. B. Kagan, J. C. Fiaud, *Top. Stereochem.* **1988**, *18*, 249; b) J. M. Keth, J. F. Larrow, E. N. Jacobsen, *Adv. Synth. Catal.* **2001**, *343*, 5; c) A. H. Hoveyda, M. T. Didiuk, *Curr. Org. Chem.* **1998**, *2*, 537.
[7] For an overview: a) *Catalytic Asymmetric Synthesis* (Ed.: I. Ojima), Wiley-VCH, New York, **2000**; b) *Comprehensive Asymmetric Catalysis* (Eds.: E. N. Jacobsen, H. Yamamaoto, A. Pfaltz), Springer, Berlin, **1999**; c) R. Noyori, *Asymmetric Catalysis in Organic Synthesis*, Wiley, New York, **1994**.
[8] W. S. Knowles, M. J. Sebacky, *J. Chem. Soc., Chem. Commun.* **1968**, 1445.
[9] T. Katsuki, K. B. Sharpless, *J. Am. Chem. Soc.* **1980**, *102*, 5974.
[10] a) M. Kitamura, T. Ohkuma, S. Inoue, N. Sayo, H. Kumobayashi, S. Akutagawa, T. Ohta, H. Takaya, R. Noyori, *J. Am. Chem. Soc.* **1988**, *110*, 629; b) R. Noyori, *Science* **1990**, 248.
[11] H. U. Blaser, F. Spindler, M. Studer, *Appl. Catal. A: General* **2001**, *221*, 119.

Knowles and his co-workers succeded in developing an effective chiral catalyst for the synthesis of the amino acid L-DOPA which is useful in the treatment of Parkinson´s disease.[8] Basically, it consists of a complex of rhodium and a chiral chelating diphosphines able to catalyze the asymmetric hydrogenation of α-acylaminoacrylic acids with high enantiomeric excess (Scheme 1). This process found application in the industrial synthesis of L-DOPA by Monsanto.[12]

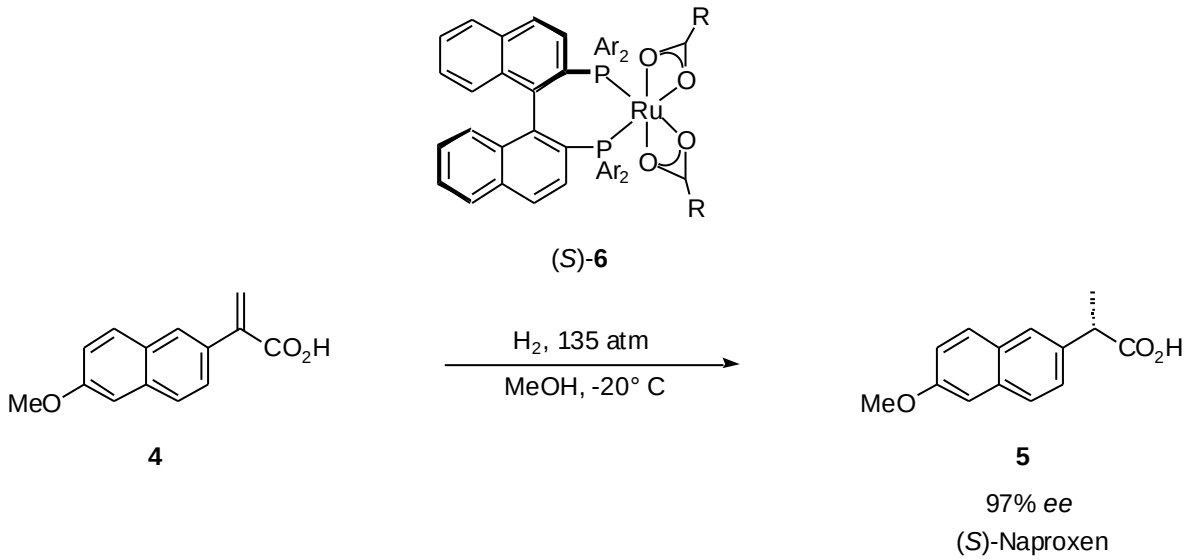


1 **2** 95% *ee* **3**

Scheme 1 Synthesis of the amino acid L-DOPA.

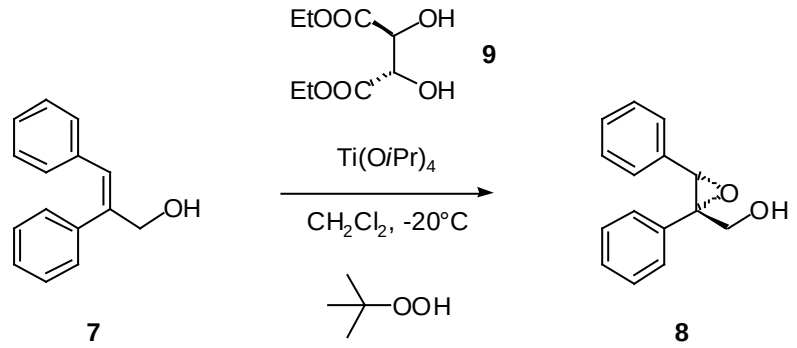
Noyori´s contribution concerns asymmetric hydrogenation reactions, catalyzed for instance by a mononuclear dicarboxylate ruthenium-BINAP complex (*S*)-**6**. The asymmetric variant proposed by Noyori has been scaled up for industrial use, e.g. in the production of (*R*)-1,2-propanediol for the synthesis of the antibiotic levofloxacin. Scheme 2 shows another application of Noyori's stereoselective reduction, namely the synthesis of the (*S*)-enantiomer of Naproxen which is an antiinflammatory and analgesic agent.

[12] W. S. Knowles, *Acc. Chem. Res.* **1983**, *16*, 106.



Scheme 2 Ruthenium-BINAP complex for asymmetric hydrogenation.

Sharpless' contribution in the field of oxidation chemistry is outstanding: in 1980 he discovered a practical method for the enantioselective epoxidation of allylic alcohols to chiral epoxides with high enantiomeric excesses by using a hydroperoxide and a chiral catalyst derived from titanium isopropoxide and optically active tartrate ester as chiral ligand (Scheme 3).[9] This system is capable of epoxidizing a wide variety of allylic alcohols in good yield and with an enantiomeric excess usually greater than 90%.

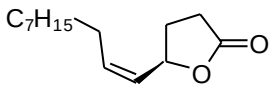


Scheme 3 Sharpless epoxidation of allylic alcohols.

The pionieering work of these scientists has found various applications and the great significance of their discoveries and improvements for industry should be enphasized. New drugs are the most important application but also production of flavouring and sweetening agents and insecticides. This year´s Nobel Price in Chemistry shows that the step from basic reasearch to industrial application could sometimes be a short one.

1.2 γ-Butyrolactones: challenging targets in organic synthesis

As already mentioned in the chapter before, chirality can play a critical role in the biological activity of molecules. A large class of chiral compounds for which this phenomenon is important comprises γ-butyrolactones which often occur in enantiomerically pure form in nature. As an example may serve the sex pheromone produced by the female Japanese beetle, *popillia japonica*, which has been identified as (*R*)-(–)-(*Z*)-5-tetradecen-4-olide (**10**) (Figure 1). As little as 1% of the *S*,*Z* isomer can significantly reduce the response of male beetles to the *R*,*Z* isomer.[13]



10

Figure 1 Sex pheromone of a female Japanese beetle.

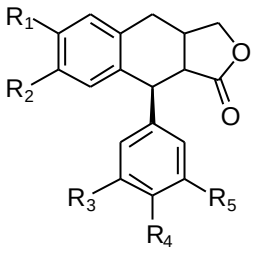
Chiral substituted γ-butyrolactones, such as the Japanese beetle pheromone, are found throughout nature in a variety of natural products. On the other hand, the γ-butyrolactone subunit has turned out to be a valuable building block for the synthesis of various natural products and biologically important substances,[14] such as alkaloids,[15] macrocyclic antibiotics, lignan lactones,[16] antileukemics, flavour components and said pheromones. Additionally, the pharmacology of substituted γ-butyrolactones is notable because they are potent antagonists or agonists, depending upon the subtitution pattern of the γ-aminobutyric acid (GABA) receptor, the major inhibitory neurotransmitter receptor in the mammalian central nervous system.[17]

Accordingly there are a large number of methods of preparation of substituted γ-butyrolactones:[18] from simple natural products such as aminoacids, tartaric acids, ascorbic

[13] E. L. Clennan, P. C. Heah, *J. Org. Chem.* **1981**, *46*, 4107.
[14] S. S. C. Koch, A. R. Chamberlin, *J. Org. Chem.* **1993**, *58*, 2725.
[15] a) Y. Ohfune, K. Hori, M. Sakaitani, *Tetrahedron Lett.* **1986**, 6079; b) S. Takano, C. Kasahara, K. Ogasawara, *Chem. Lett.* **1982**, 631; c) J. Meinwald, J. Huang, *J. Am. Chem. Soc.* **1981**, *103*, 861.
[16] a) H. Kosugi, K. Tagami, A. Tagahashi, H. Kanna, H. Uda, *J. Chem. Soc. Perkin Trans 1.* **1989**, 935; b) A. Pelter, R. S. Ward, D. M. Jones, P. Maddocks, *J. Chem. Soc. Perkin Trans. 1* **1993**, 2621; for a review, see: c) R. S. Ward, *Tetrahedron* **1990**, *46*, 5029.
[17] a) C. H. Jarboe, L. A. Porter, *J. Med. Chem.* **1968**, *11*, 729; b) E. J. Corey, H. L. Pearce, *J. Am. Chem. Soc.* **1979**, *101*, 5841.
[18] For a review, see: S. Kano, S. Shibuya, T. Ebata, *Heterocycles* **1980**, *14*, 661.

acids, carbohydrates, or ribonolactones; from chiral sulfoxide, epoxide or substituted acetylenic acids and by various enzymatic or synthetic reductions, oxidations and hydrolyses.

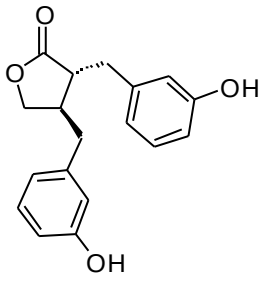
Lignans display a wide range of biological activity. Thus, deoxypodophyllotoxin and its dimethyl derivative **11** (Figure 2), which show powerful and specific cytotoxy activity, are used clinically against small cell lung cancer and testicular cancer.



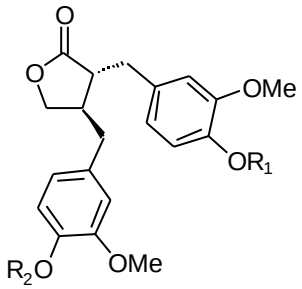
11
Deoxypodophyllotoxin

Figure 2 Lignan lactone.

Lignans are long been recognized as challenging targets for organic synthesis due to the varied structures which they possess. They also represent valuable target molecules for asymmetric synthesis due to the close juxtaposition and clearly defined relative configuration of the chiral centers present.



12
(−)-enterolactone



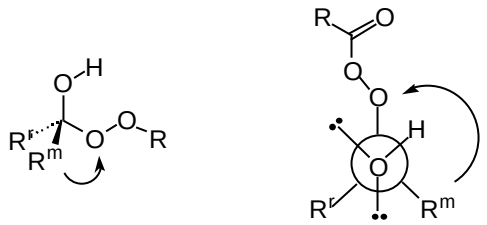
13
R_1 = H; R_2 = Me (−)-arctigenin
R_1 = Me; R_2 = H (−)-isoarctigenin

Figure 3 Natural products derived from γ-butyrolactones.

Natural products containing the butyrolactone skeleton continue to attract considerable attention due to their interesting biological profile. For example, enterolactone (**12**) (Figure 3), a lignan present in human urine, has been shown to possess protective properties toward certain types of cancer. Arctigenin **13**, another example of a bisbenzylbutyrolacton lignan, exibits anti-HIV properties.

1.3 General mechanistic aspects of the Baeyer-Villiger rearrangement

In 1899, Baeyer and Villiger first reported their method for converting ketones into esters.[19] In the 100 years since Baeyer and Villiger's discovery, the reaction that nowadays bears their names has become a milestone in organic synthesis and has found entry into standard textbooks of organic chemistry.[20] The popularity of this transformation is due chiefly to the uniqueness of the rearrangment it involves. However, the conservation of stereogenic information and a predictable regioselectivity are also important aspects of the Baeyer-Villiger oxidation. With few exceptions, the substituent vicinal to the carbonyl group that can best stabilize a partial positive charge has the higher propensity to migrate. A two-step mechanism proposed by Criegee for the Baeyer-Villiger reaction is now widely accepted. In the first reversible step a peroxy species attacks the carbonyl carbon, thereby forming a tetrahedral adduct **14a** − the so-called Criegee intermediate − which subsequently rearranges in a second step to regenerate the carbonyl function (Figure 4).[21]



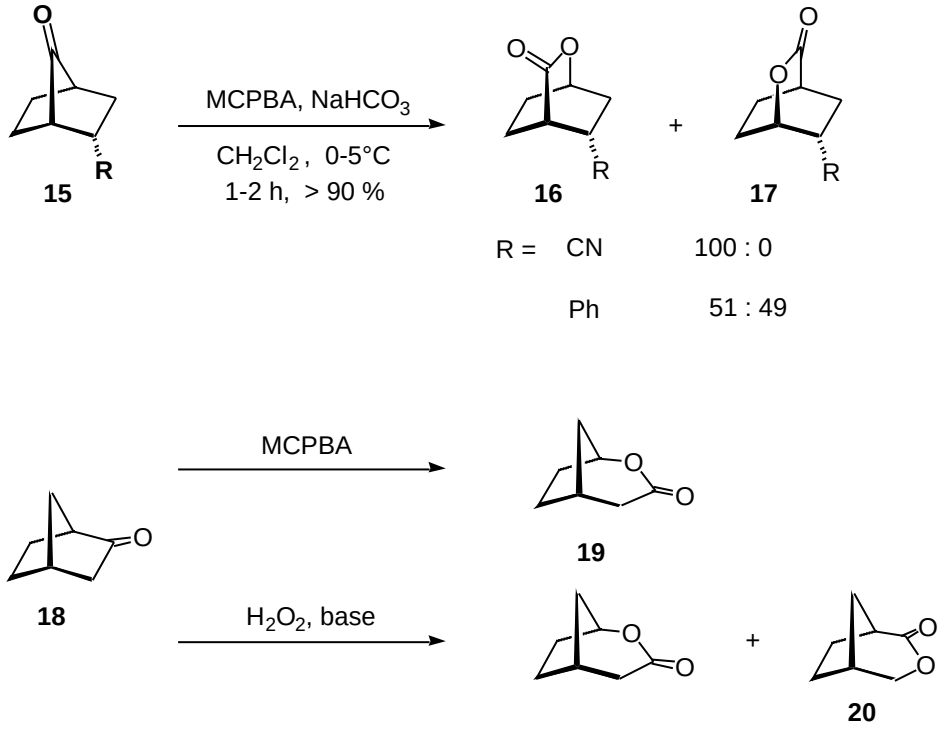
14a **14b**

Figure 4 In a tetrahedral Criegee intermediate (shown), R^m rearranges and simultaneously the reduced oxidant (ROH or RCOOH) is cleaved whereby the carbonyl group is regenerated.

In 1980, Noyori described the oxidation of a rigid bicyclic substrate which was a clear demonstration that in the Criegee intermediate a lone pair on the former carbonyl oxygen must be aligned antiperiplanar with the migrating group R^m.[22] A further stereoelectronic

[19] A. Baeyer, V. Villiger, *Ber. Dtsch. Chem. Ges.* **1899**, *32*, 3625.
[20] For reviews on the Baeyer-Villiger oxidation in general, see: a) C. H. Hassal, *Org. React.* **1957**, *9*, 73; b) G. R. Krow, *Tetrahedron* **1981**, *37*, 2697; c) G. R. Krow, *Org. React.* **1993**, *43*, 251; d) C. Bolm in *Advances in Catalytic Processes, Vol. 2* (Ed.: M. P. Doyle), JAI Press; Greenwich, **1997**, S. 43; e) M. Renz, B. Meunier, *Eur. J. Org. Chem.* **1999**, 737.
[21] R. Criegee, *Justus Liebigs Ann. Chem.* **1948**, *560*, 127.
[22] a) R. Noyori, T. Sato, H. Kobayashi, *Bull. Chem. Soc. Jpn.* **1983**, *56*, 2661; see also: b) V. Alphand, R. Furstoss, *J. Org. Chem.* **1992**, *57*, 1306; c) C. M. Crudden, A. C. Chen, L. A. Calhoun, *Angew. Chem.* **2000**, *112*, 2973; *Angew. Chem. Int. Ed.* **2000**, *39*, 2851.

requirement is the correct antiperiplanar alignment of the migrating group R^m and the O-O bond of the leaving group. The possibility of free alignment within the tetrahedral adduct given, the regioselectivity of the O-insertion may easily be predicted: the tendency to migrate falls according to the sequence of alkyl substituents R^m tertiary > secondary > primary > CH_3.[23] In general, the potential of a substituent to compensate for positive charge generated in the transition state favours its migrating.[24] A further key feature of the rearrangement lies in the retention of configuration of the migrating moiety.[25] Thus, in multistep asymmetric syntheses, a Baeyer-Villiger oxidation can be applied after the asymmetric information has been introduced into the carbonyl substrate. As regards regioselectivity, substituents located further remote from the carbonyl group may also affect the outcome of the rearrangement electronically. The oxidation of substituted norbornan-7-one **15** with m-chloroperbenzoic acid (MCPBA) represents evidence for this phenomenon.[26] With an electron-withdrawing cyano substituent in β-position to the carbonyl carbon an oxygen insertion takes place exclusively on the side that is opposite to the one bearing the substituent (Scheme 4). However, with the *endo*-substituent being a phenyl group, the formation of either regioisomeric lactone amounts to nearly the same level.



Scheme 4 Control of the regioselectivity in Baeyer-Villiger reactions.

[23] a) R. W. White, W. D. Emmons, *Tetrahedron* **1962**, *17*, 31; b) M. F. Hawthorne, W. D. Emmons, K. S. McCallum, *J. Am. Chem. Soc.* **1958**, *80*, 6393; c) W. D. Emmons, G. B. Lucas, *J. Am. Chem. Soc.* **1955**, *77*, 2287.
[24] W. E. von Doering, L. Speers, *J. Am. Chem. Soc.* **1950**, *72*, 5515.
[25] K. Mislow, J. Brenner, *J. Am. Chem. Soc.* **1953**, *75*, 2318.
[26] G. Mehta, N. Mohal, *J. Chem. Soc. Perkin Trans. 1* **1998**, 505.

The nature of the oxidizing agent also influences the regiochemistry. When, for instance, norbornan-2-one (**18)** is oxidized with MCPBA, the new C-O bond is formed at the bridgehead carbon only; yet, with H_2O_2 as oxidant in a basic medium the methylene group migrates as well and, hence, the product mixture contains either lactone.[20b]

1.4 Non-enzymatic asymmetric Baeyer-Villiger reactions

Metals are frequently employed in Baeyer-Villiger oxidations.[27] An objective of modern chemistry is to exploit metals also for an asymmetric variant of this reaction, thereby surmounting the limitations of enzymatic procedures. When a metal is used it may serve in different ways to promote the oxidation: Lewis-acid metals can catalyze both the attack of a peroxy species to the carbonyl group and the subsequent rearrangment.[28,29] Furthermore, they may play a catalytic role in the in-situ formation of an oxidant. Thus, the presence of nickel, copper or iron has proved suitable for the generation of an oxidizing agent effective in Baeyer-Villiger oxidations when oxygen was combined with an aldehyde, presumably with the intermediate appearance of acyl radicals and peracids.[30]

Oxygen could be utilized together with an aldehyde as co-reductant in Baeyer-Villiger oxidations catalyzed by nickel or copper salts. By means of these catalyses substituted cyclohexanones such as **21** (Scheme 5) were converted to the corresponding oxepanones in good yields.[31] The subsequent development of a chiral catalyst led to the copper complex (*S*,*S*)-**23**: among numerous variants this complex with two bidentate ligands of the salox type turned out to be the best one for the aerobic oxidation of ketones to lactones in an enantioselective manner.[32,33,34,35,36]

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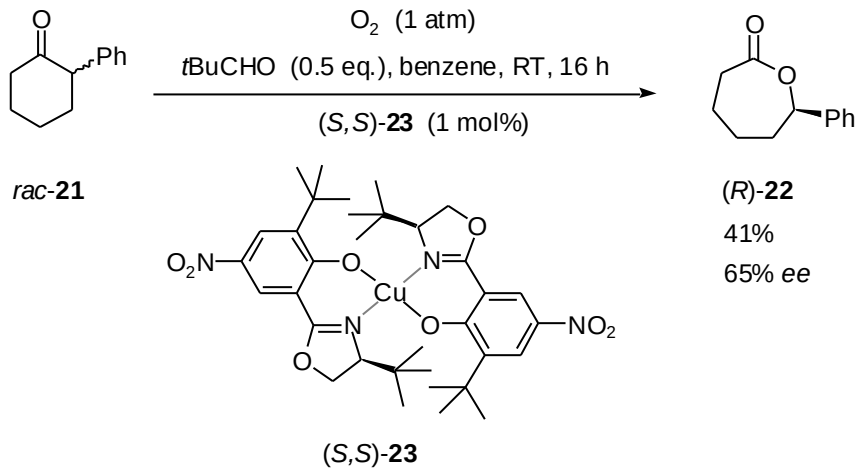
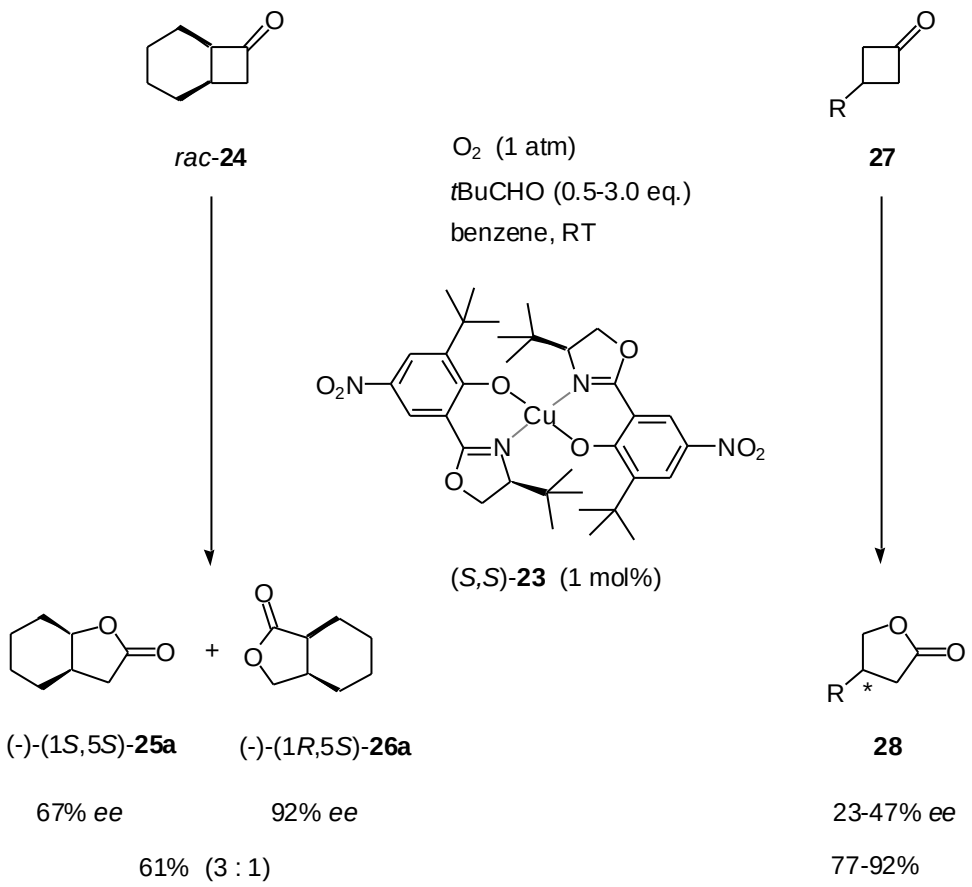
[27] See for an example of a new development with industrial relevance: A. Corma, L. T. Nemeth, M. Renz, S. Valencia, *Nature* **2001**, *412*, 423.
[28] R. Göttlich, K. Yamakoshi, H. Sasai, M. Shibasaki, *Synlett* **1997**, 971.
[29] a) S. Matsubara, K. Takai, H. Nozaki, *Bull. Chem. Soc. Jpn.* **1983**, *56*, 2029; b) M. Suzuki, H. Takada, R. Noyori, *J. Org. Chem.* **1982**, *47*, 902.
[30] a) T. Yamada, K. Takahashi, K. Kato, T. Takai, S. Inoki, T. Mukaiyama, *Chem. Lett.* **1991**, 641; b) S.-I. Murahashi, Y. Oda, T. Naota, *Tetrahedron Lett.* **1992**, *33*, 7557; c) T. Mukaiyama, T. Yamada, *Bull. Chem. Soc. Jpn.* **1995**, *68*, 17; d) J. R. McNesby, C. A. Heller, *Chem. Rev.* **1954**, *54*, 325; e) B. Phillips, F. C. Frostick, P. S. Starcher, *J. Am. Chem. Soc.* **1957**, *79*, 5982; f) D. R. Larkin, *J. Org. Chem.* **1990**, *55*, 1563.
[31] C. Bolm, G. Schlingloff, K. Weickhardt, *Tetrahedron Lett.* **1993**, *34*, 3405.
[32] a) C. Bolm, G. Schlingloff, K. Weickhardt, *Angew. Chem.* **1994**, *106*, 1944; *Angew. Chem. Int. Ed.* **1994**, *33*, 1848; b) C. Bolm, G. Schlingloff, *J. Chem. Soc. Chem. Commun.* **1995**, 1247; c) C. Bolm, T. K. K. Luong, G. Schlingloff, *Synlett* **1997**, 1151; d) C. Bolm, G. Schlingloff, F. Bienewald, *J. Mol. Cat.* **1997**, *117*, 347.
[33] K. Weickhardt, Dissertation, University of Basel, **1993**.
[34] G. Schlingloff, Dissertation, Philipps University of Marburg, **1995**.



Scheme 5 The first asymmetric Baeyer-Villiger reaction, catalyzed by a chiral copper complex.

Racemic cyclohexanones with different aromatic substituents in α-position were oxidized in the presence of 1 mol% if (*S*,*S*)-**23** to nonracemic lactones. Thus, starting from 2-phenylcyclohexanone (*rac*-**21**) the oxepanone (*R*)-**22** could be obtained with 41% yield and 65% *ee*. This was a first example of a metal-catalyzed asymmetric Baeyer-Villiger oxidation.[37] Besides the use of pivaldehyde as co-reductant, both the aromatic *p*-nitro substituent in complex **23** and the sterically demanding *tert*-butyl group at the 4,5 dihydrooxazol ring proved essential. Moreover, Cu-complexes with tetradentate salen ligands displayed no catalytic activity. For this observation, one could assume that in the case of bidentate salox ligands a hypothetical peroxy species formed during the catalysis would replace one salox ligand at the central metal. The assumption, in turn, that peroxy radicals or peracids be involved in the metal catalysis was suggested by a successful enantioselective oxidation with lauryl peracid instead of dioxygen and aldehyde. A drawback of the catalytic system (*S*,*S*)-**23**/pivaldehyde/oxygen is the limitation to 2-aryl-substituted cyclohexanones. The position isomer 4-phenyl cyclohexanone or 2-alkyl-substituted cyclohexanones are not converted to lactones.

[35] T. K. K. Luong, Dissertation, RWTH, Aachen University, **1998**.
[36] O. Beckmann, Diplom thesis, RWTH, Aachen University, **1997**.
[37] Reviews on metal-mediated asymmetric Baeyer-Villiger oxidations: a) C. Bolm, O. Beckmann, T. K. K. Luong in *Transition Metals for Organic Synthesis, Vol. 2* (Eds.: M. Beller, C. Bolm), Wiley-VCH, Weinheim, **1998**, S. 213; b) G. Strukul, *Angew. Chem.* **1998**, *110*, 1256; *Angew. Chem. Int. Ed.* **1998**, *37*, 1198; d) C. Bolm, O. Beckmann in *Comrehensive Asymmetric Catalysis, Vol. 2* (Eds.: E. N. Jacobsen, A. Pfaltz, H. Yamamoto), Springer, Berlin, **1999**, S. 803.



Scheme 6 Cu-catalyzed oxidation of racemic or prochiral cyclobutanones.[38]

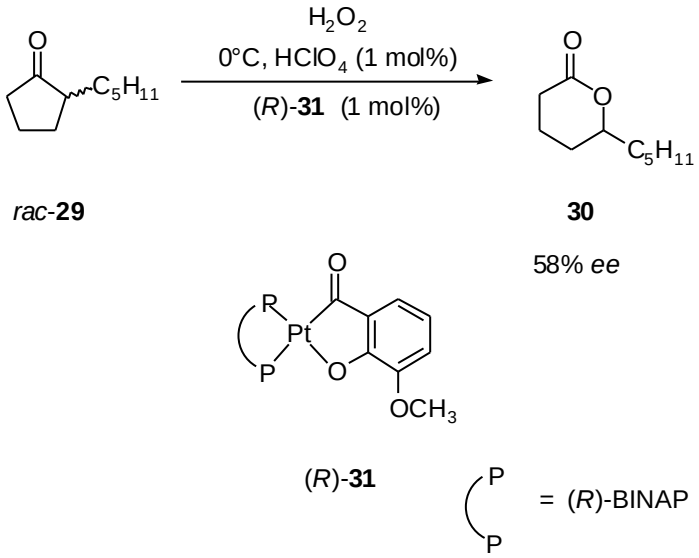
Cyclobutanones would readily react under the conditions of the catalysis to γ-butyrolactones which represent valuable intermediates in the asymmetric synthesis of various pharmaceuticals and natural products − a reactivity which can be attributed to their inherent ring strain.[39] Thus, the reaction of racemic *cis*-bicyclooctanone *rac*-**24** yielded 61% of the two regioisomeric lactones **25a** and **26a** in a ratio of 3 to 1 (Scheme 6). The oxidation of *rac*-**24** obviously proceeds in an enantiodivergent manner, i.e. the regioisomeric lactones **25a** and

[38] Stereochemical convention: in accordance with the propositions made by Maehr all absolute configurations of stereogenic centres are graphically represented by wedges throughout the present thesis. In contrast, bars are employed to depict racemates graphically. Cf.: H. Maehr, *J. Chem. Educ.* **1985**, *62*, 114.

[39] A selection of examples involving γ-butyrolactones: a) H. Kosugi, K. Tagami, A. Takashi, H. Kanna, H. Uda, *J. Chem. Soc. Perkin Trans. 1* **1989**, 935; b) A. Pelter, R. S. Ward, D. M. Jones, P. Maddocks, *J. Chem. Soc. Perkin Trans. 1* **1993**, 2621; c) S. S. Canan Koch, A. R. Chamberlin, *J. Org. Chem.* **1993**, *58*, 2725; d) M. P. Doyle, M. N. Protopopova, Q.-L. Zhou, J. W. Bode, S. H. Simonsen, V. Lynch, *J. Org. Chem.* **1995**, *60*, 6654; e) Shiotani, H. Okada, T. Yamamoto, K. Nakamata, J. Adachi, H. Nakamoto, *Heterocycles* **1996**, *43*, 113; f) C. Mazzini, J. Lebreton, V. Alphand, R. Furstoss, *Tetrahedron Lett.* **1997**, *38*, 1195; g) A. Krief, A. Ronvaux, A. Tuch, *Bull. Soc. Chim. Belg.* **1997**, *106*, 699; h) K. Hirayama, K. Mori, *Eur. J. Org. Chem.* **1999**, 2211; i) B. M. Trost, Y. H. Rhee, *J. Am. Chem. Soc.* **1999**, *121*, 11680; j) Y. Takaya, T. Senda, H. Kurushima, M. Ogasawara, T. Hayashi, *Tetrahedron: Asymmetry* **1999**, *10*, 4047; k) G. Fardella, P. Barbetti, G. Grandolini, I. Chiappini, V. Ambrogi, V. Scarcia, A. Furlani Candiani, *Eur. J. Med. Chem.* **1999**, *34*, 515; l) D. Takano, M. Doe, Y. Morimoto, K. Yoshihara, T. Kinoshita, *J. Heterocyclic Chem.* **1999**, *36*, 221; m) N. Gathergood, K. A. Jørgensen, *Chem. Commun.* **1999**, 1869; n) E. J. Bergner, G. Helmchen, *Eur. J. Org. Chem.* **2000**, 419.

26a are chiefly produced from different enantiomers of the racemic ketone.[40,41] The prochiral 3-substituted cyclobutanones with alkyl, aryl or carboxylato substituents only gave modest *ee* values of up to 47% after the catalytic oxidation. Increasing the amount of pivaldehyde, one could obtain higher yields with the enantioselectivity unchanged.

Independently and at the same time as the described copper system another catalytic method for the asymmetric Baeyer-Villiger oxidation was derived. Strukul et al. found that a cationic Pt-diphosphine complex allowed the oxidation of ketones with H_2O_2.[42] The highest enantiomeric excess of 58% was attained upon partial conversion of 2-(*n*-pentyl)-cyclopentanone (*rac*-**29**) in the presence of BINAP/vanilline platinum complex (*R*)-**31** (Scheme 7). A comparison with the reaction of 2-methyl cyclopentanone revealed that a shorter side chain in the substrate brought about a higher reaction rate and a lower enantioselectivity.



Scheme 7 Platinum-catalyzed asymmetric Baeyer-Villiger oxidation.

The catalytically active cationic species is generated by the reaction of **31** with $HClO_4$. The phenolic oxygen is protonated, thereby breaking its bond to the metal. As against to the treatment of **31** with HCl which leads to an inactive chloro complex, the non-coordinating

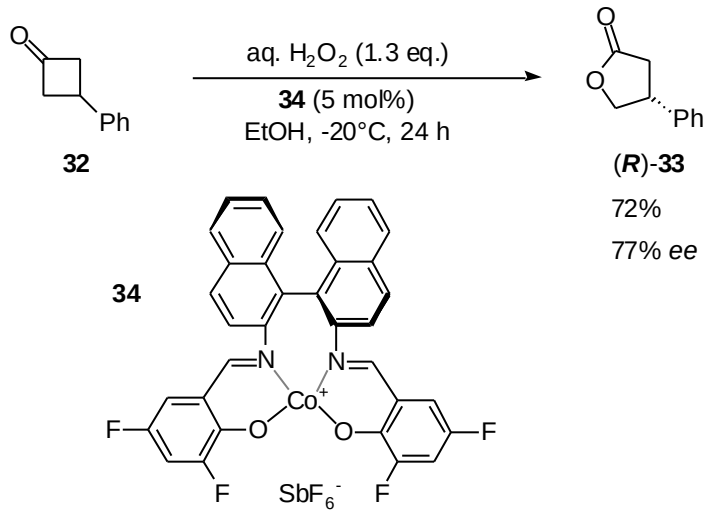
[40] Cf. this phenomenon in microbiological transformations: a) C. T. Walsh, Y.-C. J. Chen, *Angew. Chem.* **1988**, *100*, 342; *Angew. Chem. Int. Ed. Engl.* **1988**, *27*, 333; b) V. Alphand, A. Archelas, R. Furstoss, *Tetrahedron Lett.* **1989**, *30*, 3663; c) V. Alphand, R. Furstoss, *J. Org. Chem.* **1992**, *57*, 1306.

[41] For a mathematical model describing this and other reactions, see: H. B. Kagan, *Croatica Chem. Acta* **1996**, *69*, 669.

[42] a) C. Paneghetti, R. Gavagnin, F. Pinna, G. Strukul, *Organometallics* **1999**, *18*, 5057; b) R. Gavagnin, M. Cataldo, F. Pinna, G. Strukul, *Organometallics* **1998**, *17*, 661; c) G. Strukul, A. Varagnolo, F. Pinna, *J. Mol. Catal.* **1997**, *117*, 413; d) A. Gusso, C. Baccin, F. Pinna, G. Strukul, *Organometallics* **1994**, *13*, 3442.

anion ClO_4^- leaves a coordinative site at the Pt-atom vacant whereby the central metal gains its catalytic activity.

Very recently, a catalytic variant using cobalt was reported.[43] Uchida and Katsuki found Co(III)(salen) complex **34** to be efficient as catalyst for asymmetric Baeyer-Villiger oxidations of 3-substituted cyclobutanones when used in combination with hydrogen peroxide as terminal oxidant.

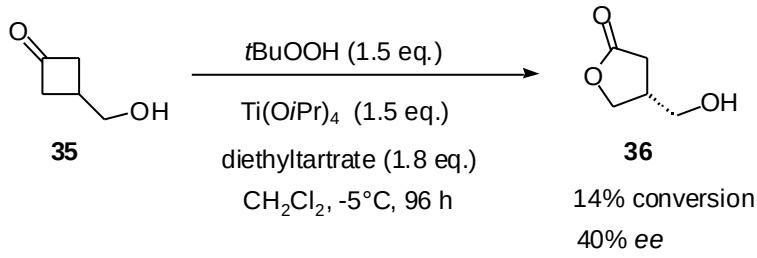


Scheme 8 Katsuki's asymmetric cobalt catalysis with hydrogen peroxide.

The efficiency of this cobalt-catalyst was assumed to rely on the *cis*-β structure of the Co-complex bearing two vicinal coordinating sites that become vacant during catalysis. With the two cis sites of the metal coordinating to a peroxy species and to the carbonyl substrate, respectively, the second peroxygen may attack the carbonyl carbon, thus forming a five-membered chelate ring. Such a ring in the transition state would represent a chelate Criegee adduct which obviously imposes considerable enantioselectivity, i.e. up to 77% *ee* with 72% yield for cyclobutanone (*S*)-**33**.

Besides the three catalytic versions described above, a few methods were derived that used stoichiometric amounts of metal and chiral ligand, respectively. Kanger et al., for instance, applied Sharpless' system for allylic epoxidations, Ti(O*i*Pr)$_4$/DET/TBHP, to cyclobutanones (Scheme 9).[44]

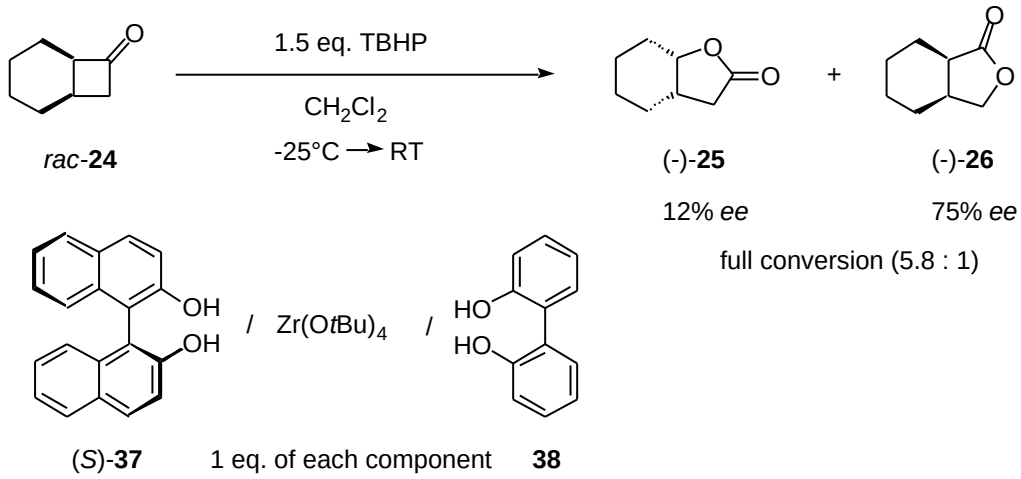
[43] T. Uchida, T. Katsuki, *Tetrahedron Lett.* **2001**, *42*, 6911.
[44] a) T. Kanger, K. Kriis, A. Paju, T. Pehk, M. Lopp, *Tetrahedron: Asymmetry* **1998**, *9*, 4475; b) M. Lopp, A. Paju, T. Kanger, T. Pehk, *Tetrahedron Lett.* **1996**, *37*, 7583.



Scheme 9 Baeyer-Villiger oxidation using the Sharpless system for epoxidation.

Up to 75% *ee* was attained in the presence of stoichiometric and overstoichiometric amounts of Ti-DET. In this oxidation reaction the conversion remained modest, the maximum being 49%.

The homologue of titanium, zirconium, could also be utilized for the promotion of the asymmetric rearrangement according to an observation by Bolm and Beckmann.[45] In the stoichiometric presence of a species generated in situ from Zr(O*t*Bu)$_4$ and 2 eq. of enantiopure BINOL cyclobutanones were oxidized quantitatively with TBHP, the resulting lactones however displaying only modest *ee* values.



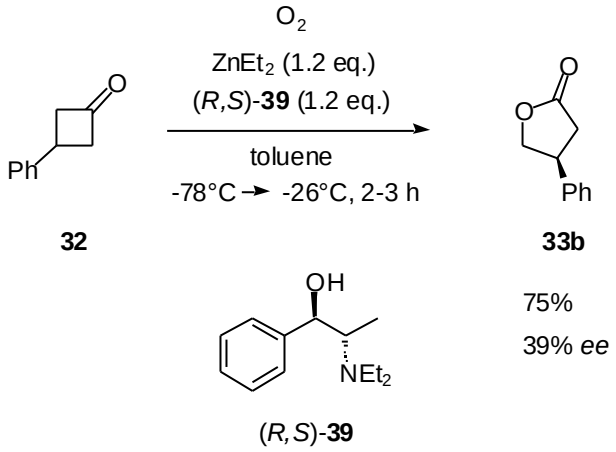
Scheme 10 Zr-based promotion of enantioselective Baeyer-Villiger oxidations.

Interestingly, one equivalent of the BINOL ligand proved to be dispensable when it was replaced by the proatropisomeric compound biphenol (Scheme 10). Apparently, the remaining BINOL molecule bound to zirconium induced its chirality onto the axially flexible biphenol,

[45] C. Bolm, O. Beckmann, *Chirality* **2000**, *12*, 523.

thereby keeping the *ee* values of the products at the same level. Another feature of this system is the dependence of the upshot as regards enantioselectivity on the time allowed for the preforming of the Zr-BINOL species, indicating equilibrium reactions between complexes of different efficiency.

Also with the (over)stoichiometric use of metal and chiral ligand, Kotsuki et al. made 3-phenyl cyclobutanone (**32**) react to the lactone **33b** (Scheme 11).[46]

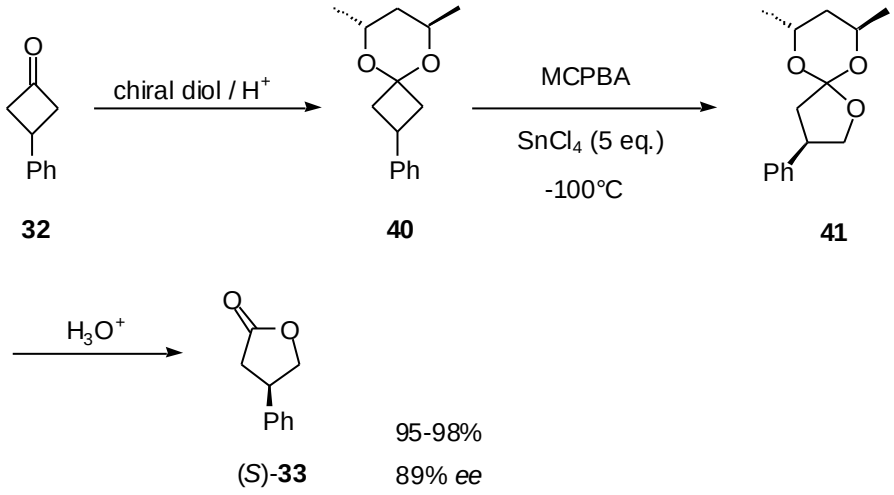


Scheme 11 Zinc-mediated oxidation with oxygen.

With this system, which originates from a method derived by Enders et al. for enone epoxidation,[47] dioxygen could be utilized as oxidizing agent in combination with $ZnEt_2$ and amino alcohol (*R*,*S*)-**39**. Lactones of up to 39% *ee* could be obtained in good yields starting from substrate **32**.

Sugimura et al. introduced the diastereotopically distinguishing oxidation of ketales such as **40**. This reaction led to lactones with high enantioselectivities employing, however, overstoichiometric amounts of a chiral diol and $SnCl_4$ (Scheme 12).[48] While the oxidation of ketale **40** with MCPBA in dichloromethane did not proceed even upon heating under reflux, the addition of $SnCl_4$ promoted the reaction at low temperatures.

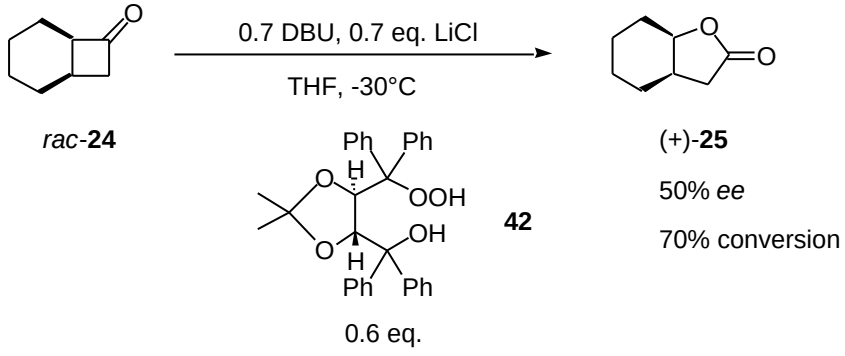
[46] T. Shinohara, S. Fujioka, H. Kotsuki, *Heterocycles* **2001**, *55*, 237.
[47] a) D. Enders, J. Zhu, G. Raabe, *Angew. Chem.* **1996**, *108*, 1827; *Angew. Chem. Int. Ed.* **1996**, *35*, 1725; b) D. Enders, J. Zhu, L. Kramps, *Liebigs Ann. Receuil* **1997**, 1101.
[48] T. Sugimura, Y. Fujiwara, A. Tai, *Tetrahedron Lett.* **1997**, *38*, 6019.



Scheme 12 Oxidation of chiral cyclobutanone ketales.

After cleavage of the chiral auxiliary enantioenriched γ-butyrolactones were afforded quantitatively. The largest *ee* value could be attained at −100 °C with a ketale derived from 3-phenylcyclobutanone (**32**) and 2,4-pentanediol. By using 5 eq. of $SnCl_4$ one obtained the corresponding lactone **33** with 89% *ee*. Lower proportions of tin reagent in the reaction mixture effected a sharp decrease of the enantiomeric excess: an oxidation using 0.5 eq. of $SnCl_4$ yielded the lactone **33** with 34% *ee* only.

An approach different from the aforementioned ones was made by Aoki and Seebach in that they synthesized a nonracemic oxidant first which was then employed under base catalysis.[49] Thus, the readily accessible TADDOL derived hydroperoxide **42** oxidized bicyclooctanone **24** to the lactone **25** with 50% *ee* exclusively (Scheme 13).



Scheme 13 The chiral TADDOL hydroperoxide **42** as nonracemic oxidant.

[49] M. Aoki, D. Seebach, *Helv. Chim. Acta* **2001**, *84*, 187.

The briefly presented methods for metal-mediated enantioselective Baeyer-Villiger oxidations known in the literature include in part impressive developments. However, the sheer low number of such methods, let alone their drawbacks and limitations which become apparent when studying the sytems in detail, reflects the fact that this type of asymmetric catalysis has not yet very much investigated. A disadvantage of the oxidations involving titanium, zirconium, zinc or tin is of course that they rely on (over)stoichiometric amounts of both the metal and the enantiopure ligand or auxiliary. The genuinely catalytic systems based on copper, platinum or cobalt partly exhibit notable enantioselectivities but they nevertheless do not yet represent a practicable tool for asymmetric synthesis.

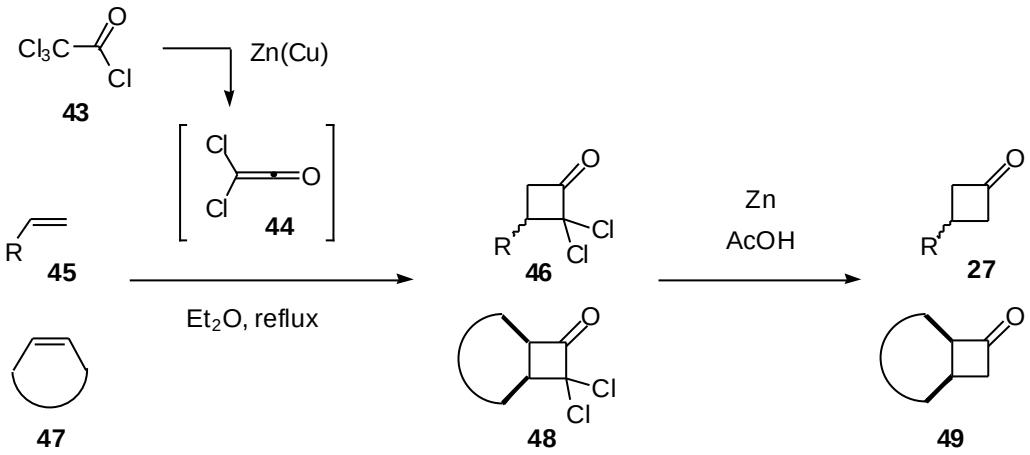
2 Research objective

The objective of the present thesis consisted of the development of novel approaches to metal-mediated asymmetric Baeyer-Villiger oxidations. Firstly, a newly established method based on aluminum was to be evaluated further. Moreover, the search for other metals that combined with chiral ligands to give an efficient oxidation system should be continued, in particular by focusing on Lewis acids that already had proved successful in metal catalysis. Apart from these studies directed towards methodic problems in asymmetric catalysis, Baeyer-Villiger oxidations in supercritical carbon dioxide were to be investigated with respect to question whether such oxidation reactions could be conducted in this advantageous solvent.

3 Results and discussion

3.1 Synthesis of the substrates

γ-Butyrolactones are a very interesting class of naturally occurring compounds which also represent useful intermediates in organic synthesis. A convenient access to them would be to synthesize such enantiomerically enriched molecules by simple asymmetric Baeyer-Villiger oxidation of cyclobutanones. Racemic bicyclic and prochiral monosubstituted cyclobutanones, in turn, are easily achievable by means of a [2+2] cycloaddition of dichloroketene and an olefin and subsequent dehalogenation (Scheme 14).[50] The dichloroketene can be formed in situ from reaction of trichloroacetyl chloride with activated zinc (zinc-copper couple) and then in the second step the *rac*-2,2'-dichloro cyclobutanone is treated with zinc in acetic acid to obtain the desired cyclobutanone.

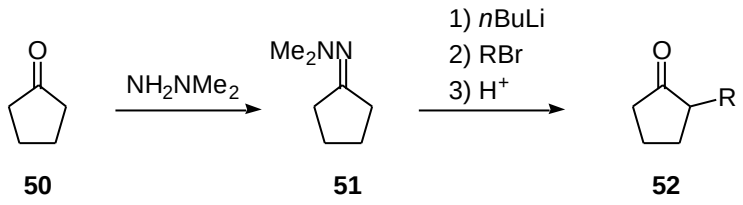


Scheme 14 Synthesis of racemic bicyclic and prochiral monosubstituted cyclobutanones.

As regards the synthesis of racemic monosubstituted substrates, alkyl derivatives were obtained in two steps (Scheme 15).[51] Firstly, *N*,*N*-dimethylhydrazone **51** was synthesized by reaction of the cycloalkanone with *N*,*N*-dimethylhydrazine in the presence of a catalytic

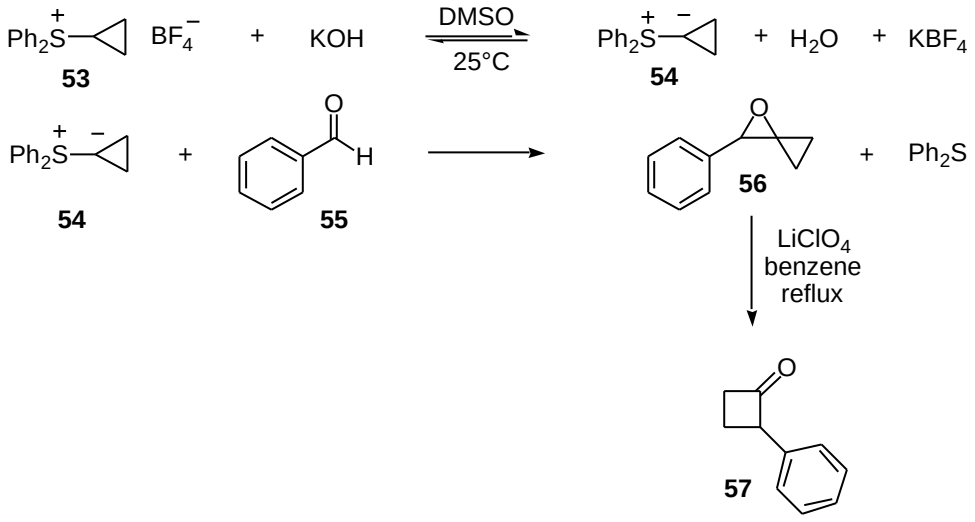
[50] a) L. Ghosez, R. Montaigne, A. Roussel, A. Vanlierde, P. Mollet, *Tetrahedron* **1971**, *27*, 615; b) L. R. Krepski, A. Hassner, *J. Org. Chem.* **1978**, *43*, 2879; c) A. Hassner, J. Dillon, Jr., *J. Org. Chem.* **1983**, *48*, 3382; d) Review: J. A. Hyatt, P. W. Raynolds, *Org. React.* **1994**, *45*, 159; e) V. Kaiwar, C. B. Reese, E. J. Gray, S. Neidle, *J. Chem. Soc. Perkin Trans. 1* **1995**, 2281.
[51] T. Mino, S. Masuda, M. Nishio, M. Yamashita, *J. Org. Chem.* **1997**, *62*, 2633.

amount of trifluoroacetic acid. The second part was the deprotonation with *n*-BuLi, alkylation with an alkylbromide and hydrolysis to obtain the desired 2-alkylcycloalkanone (**52**).



Scheme 15 Synthesis of racemic monosubstituted substrates.

Concerning the introduction of a phenyl group into position 2 of the cyclobutanone ring, a protocol reported by Trost and Bogdanowicz was used.[52] This spiroannelation procedure consisted in the reversible generation of a diphenylsulfonium cyclopropylide **54** which was obtained by treatment of cyclopropyldiphenyl-sulfonium fluoroborate **53** with powdered potassium hydroxide in dimethylsulfoxide (DMSO). Benzaldehyde reacted then easily with compound **54** to give an oxaspiropentane. Upon working up the reaction mixture with aqueous acid, the corresponding cyclobutanone was isolated directly (Scheme 16).



Scheme 16 Synthesis of 2-phenylcyclobutanone according to Trost.[52]

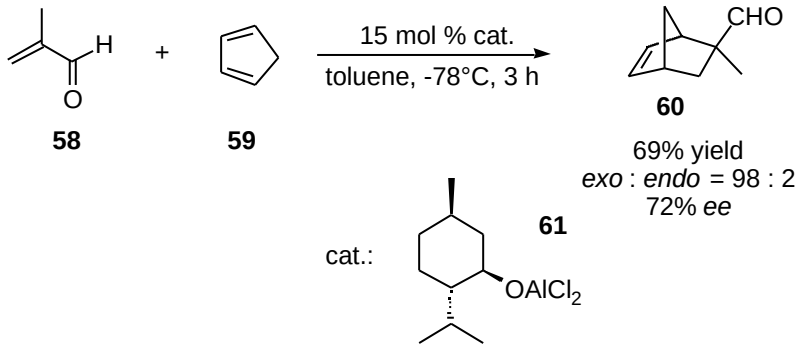
In order to have racemic standard lactones for comparison in GC analysis and for the determination of the conditions of separation of the two enantiomers with chiral gas chromatography or HPLC, all substrates were oxidized with *m*-chloroperbenzoic acid (MCPBA) in dichloromethane to the corresponding lactones which were isolated.

[52] B. M. Trost, M. J. Bogdanowicz, *J. Am. Chem. Soc.* **1973**, *95*, 5321.

3.2 Chiral aluminium complexes

3.2.1 Chiral aluminium complexes in asymmetric catalysis[53]

The earliest report of a reaction mediated by a chiral threefold coordinated aluminium species described an asymmetric Meerwein-Ponndorf-Verley reduction of ketones with a chiral aluminium alkoxide. However, this resulted in low enantiomeric excess in the alcohol products.[54] Subsequent developements were made in the field of polymerization reactions[55] with the first report presenting the polymerization of benzofurane with a catalyst prepared from ethylaluminiumdichloride and a variety of chiral ligands including amino acids. It was nearly two decades later when Koga reported that a catalyst derived from diethylaluminiumchloride and menthol catalyzed an asymmetric Diels-Alder reaction.[56]



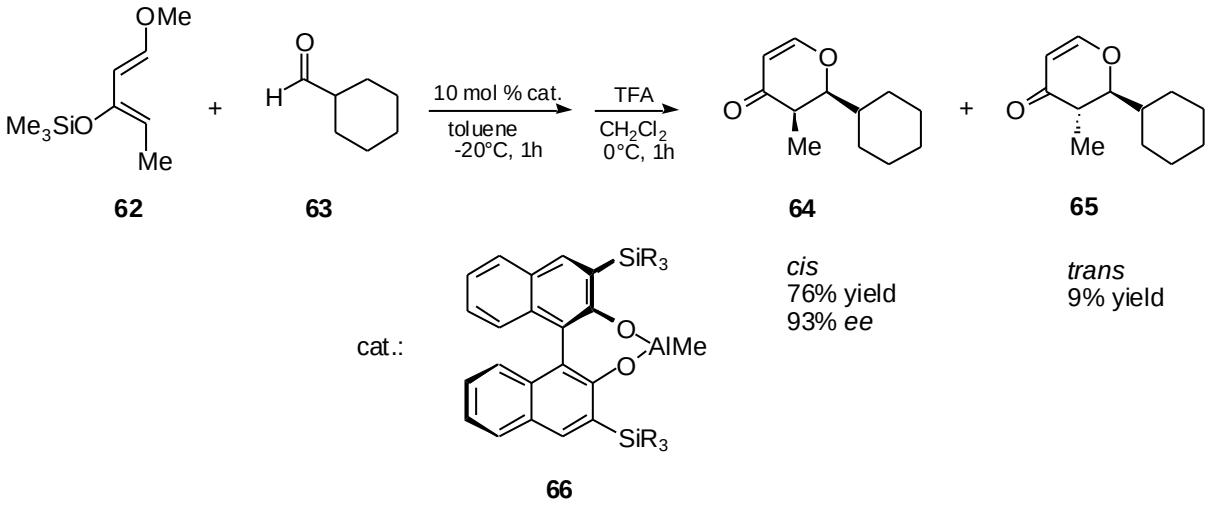
Scheme 17 Al-menthol catalyzed asymmetric Diels-Alder reaction.

Diels-Alder reactions of aldehydes are typically faster than those of esters, thus reasonable rates were observed by Kagan with a chiral aluminium catalyst in the reaction of unsaturated aldehydes with cyclopentadiene.[57] The catalyst was prepared in situ from a chiral diol and $MeAlCl_2$, the catalyst aging time being crucial for this reaction. The optimum preforming time was observed to be 3 h (resulting in 73% *ee*), while a longer aging time of 20 h led to a drop in the *ee* to 17%. On the other hand, with freshly prepared catalyst the *ee* was just 6%. Moreover, Kagan made the interesting observation that the reaction of methyl acrolein and

[53] For a review on chiral aluminium Lewis acids, see: W. D. Wulff in *Lewis Acids in Organic Synthesis* (Ed.: H. Yamamoto), Wiley-VCH: Weinheim, Germany, **2001**, p.283.
[54] W. von E. Doering, R. W. Young, *J. Am. Chem. Soc.* **1950**, *72*, 631.
[55] G Natta, M. Farina, M. Peraldo, G. Bressan, *Chim. Ind.* **1961**, *43*, 68.
[56] S.-I. Hashimoto, N. Komeshima, K. Koga, *J. Chem. Soc., Chem. Commun.*, **1979**,437.
[57] F. Rebiere, O. Riant, H. B. Kagan, *Tetrahedron: Asymmetry* **1990**, *1*, 199.

cyclopentadiene with these chiral aluminium complexes occurred with asymmetric auto-induction. In fact, at 4% conversion an enantiomeric excess of 38% was achieved for the 3-exo product. However, the *ee* increased to 73% at the end of the reaction. This implies that the catalyst changed during the course of the reaction so that the enantioselectivity gained increased with time.

A highly enantioselective hetero-Diels-Alder reaction was reported, which used a catalyst derived from 3,3´-bis-diarylsilyl BINOL and Me_3Al (Scheme 18).[58] The catalyst displayed pink to wine red colour and was found, by measurement of freezing point depression, to be a monomer.[59]



Scheme 18 BINOL-Al complex as catalyst for hetero Diels-Alder reactions.

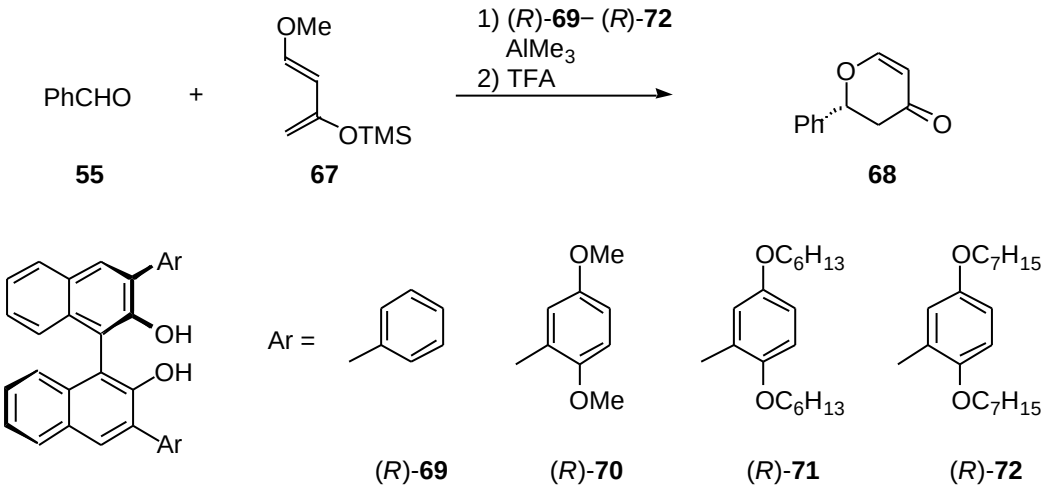
Steric effects in the BINOL ligand coordination sphere and hypercoordination of the Al centre[60] were found by Jørgensen and co-workers to be strong contributing factors with respect to the optical yield in the hetero Diels-Alder reaction between an aldehyde (**55**) and

[58] a) K. Maruoka, T. Itoh, T. Shirasaka, H. Yamamoto, *J. Am. Chem. Soc.* **1988**, *110*, 310; b) K. Maruoka, K. Nonoshita, H. Yamamoto, *Syn. Comm.* **1988**, *18*, 1453.

[59] The type of Al species – monomeric or oligomeric – apparently must be involved in the enantioselection process; cf. the discussion on Al-BINOL species in asymmetric Baeyer-Villiger oxidation (vide infra within the chapter)

[60] Hypercoordination has been shown to be of importance in several Lewis acids catalyzed addition reactions to aldehydes. See: a) K. Maruoka, T. Ooi, *Chem. Eur. J.* **1999**, *5*, 829; b) T. Ooi, D. Uraguchi, N. Nagoshima, K. Maruoka, *J. Am. Chem. Soc.* **1998**, *120*, 5327; c) T. Ooi, N. Nagoshima, K. Maruoka, *J. Am. Chem. Soc.* **1997**, *119*, 5754; d) D. P. Heller, D. R. Goldberg, W. D. Wullf, *J. Am. Chem. Soc.* **1997**, *119*, 10551; e) E. Keller, N. Veldman, A. L. Spek, B. L. Feringa, *Tetrahedron: Asymmetry* **1997**, *8*, 3403; f) T. Arai, H. Sasai, K. Yamaguchi, M. Shibasaki, *J. Am. Chem. Soc.* **1998**, *120*, 441; g) M. Murakata, T. Jono, Y. Mizuno, O. Hoshino, *J. Am. Chem. Soc.* **1997**, *119*, 11713.

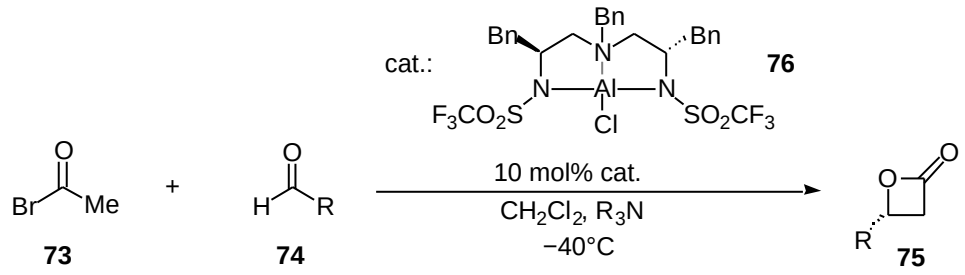
Danishefsky´s diene (**67**) (Scheme 18).[61] They prepared a series of BINOL ligands (*R*)-**69**−(*R*)-**72** with various substituents on the naphthyl ring system located close to the active centre of the catalyst with an ether substituent in position 2 and 2' of the coordinated BINOL.[62] It is reasonable to assume that one of the ether oxygens was bound to aluminium: this led to a trigonal-bipyrimidal structure at the aluminium centre which can account for the stereochemical outcome of the reaction, reported in Scheme 19, namely 99% *ee* using (*R*)-**71** as ligand. For instance, in the case of the complex derived from ligand (*R*)-**70** and trimethylaluminium, the 2,5-dimethoxyphenyl substituent, which was not involved in hypercoordination to aluminium, was oriented perpendicular to the BINOL, while the 2,5-dimethoxyphenyl substituent, which hypercoordinated to aluminium was twisted towards the metal. The twisting of the 2,5-dimethoxyphenyl substituent created a suitable chiral environment for the approach of benzaldehyde and diene.[61]



Scheme 19 Hypercoordinating chiral aluminium complexes.

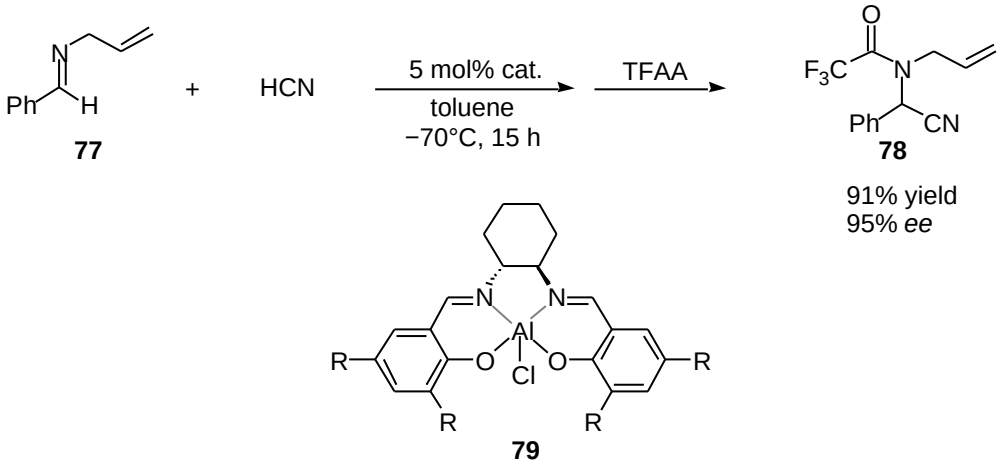
Nelson et al. described an enantioselective Al-catalyzed cyclocondensation of acyl halides and enolizable aldehydes as a strategy for catalyzed cross aldol reactions.[63] A tetracoordinate Al(III)-triamine complex **76**, as shown in Scheme 20, is the catalytically active species for the cyclocondensation of acetyl bromide **73** and benzyloxy acetaldehyde **74**, employing di(isopropyl)ethylamine (DIEA) as the base, to afford optically active β-lactone **75**.

[61] K. B. Simonsen, N. Svenstrup, M. Roberson, K. A. Jørgensen, *Chem. Eur. J.* **2000**, *6*, 123.
[62] a) K. B. Simonsen, P. Bayon, R. G. Hazell, K. V. Gothelf, K. A. Jørgensen, *J. Am. Chem. Soc.* **1999**, *121*, 3845; b) K. B. Simonsen, K. A. Jørgensen, Q.-S. Hu, L. Pu, *J. Am. Chem. Soc.* **1997**, *119*, 12454.
[63] a) S. G. Nelson, T. J. Peelen, Z. Wan, *J. Am. Chem. Soc.* **1999**, *121*, 9742 b) S. G. Nelson, B. –K. Kim, T. J. Peelen, *J. Am. Chem. Soc.* **2000**, *122*, 9318; c) Z. Wan, S. G. Nelson, *J. Am. Chem. Soc.* **2000**, *122*, 10470; d) S. G. Nelson, Z. Wan, *Org. Lett.* **2000**, *13*, 2000.



Scheme 20 Catalyzed asymmetric acyl halide-aldehyde cyclocondensation.

Aluminium salen complexes have been reported by Sigman and Jacobsen as efficient catalysts in the Strecker reaction.[64] They prepared and screened different chiral salen complexes derived from transition metals as well as main group metals, and found that the aluminium catalyst was optimum in terms of both enantioselectivity and rate of addition of trimethylsilyl cyanide to imine at room temperature (Scheme 21). This constituted the first aluminium salen complex developed for an asymmetric catalytic reaction.



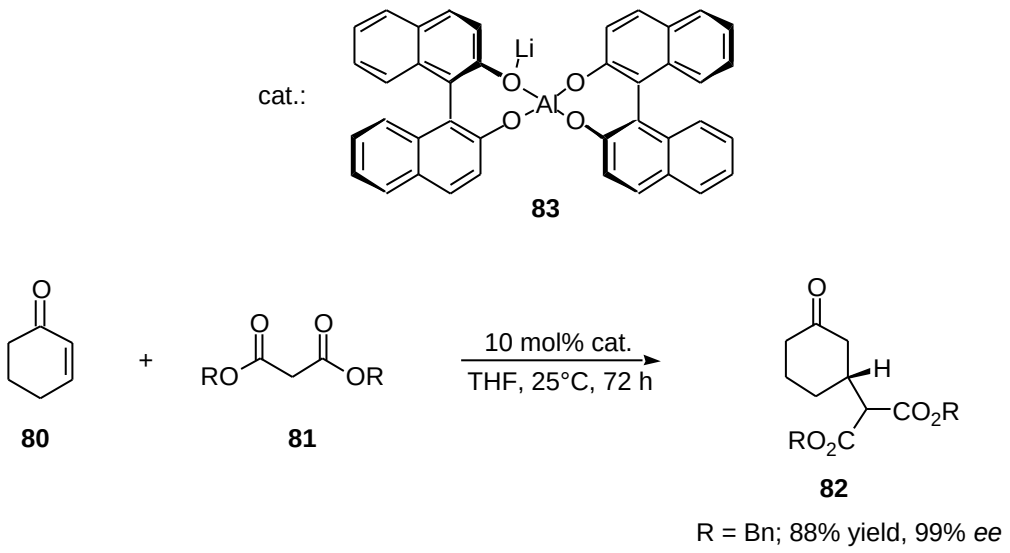
Scheme 21 Aluminium salen catalyzed Streker reaction.

3.2.2 New generation of aluminium catalysts: bifunctional catalysts

Bifunctional catalysts represent promising catalysts owing to the attachment of both electrophilic and nucleophilic substrates to the chiral catalyst in the transition state complex. This behaviour can lead to a stronger stereodiscrimination and result in a highly enantioselective process. Shibasaki et al. developed a novel chiral heterobimetallic complex prepared by addition of two equivalents of enantiopure BINOL to lithium aluminiumhydride.

[64] M. S. Sigman, E. N. Jacobsen, *J. Am. Chem. Soc.* **1998**, *120*, 5315.

This catalyst was found to have an excellent enantiodiscrimination capacity in the Michael addition of malonic esters to cyclic enones, as indicated in Scheme 22.[65] Support for coordination numbers higher than four for aluminium in this mechanism came from ^{27}Al NMR studies. The ^{27}Al NMR spectrum of the complex when 3 equivalents of enone were used was interpreted as indicative of the presence of a hexacoordinate Al coordinated to two molecules of enone. This bifunctional catalysts and anologues of it have been succesfully applied as catalysts in many other asymmetric tranformations, i.e. C-C, C-S, C-P, C-O and C-H bond-forming reactions.[66]

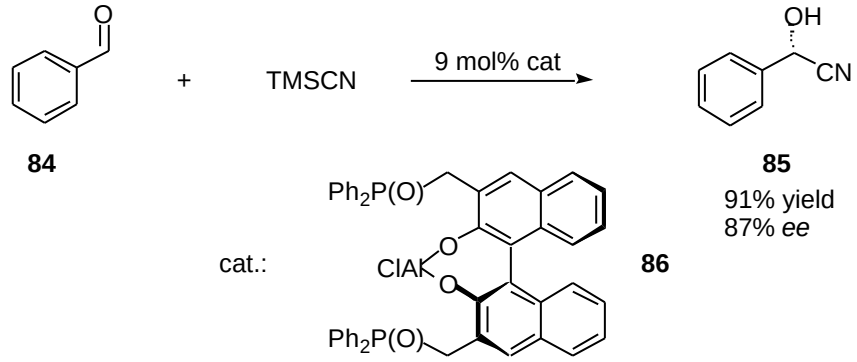


Scheme 22 Shibasaki's chiral heterobimetallic complex.

The concept of bifunctional catalysts has been extended by Shibasaki to another class of compounds, viz monometallic, phosphinoyl-containing catalysts with both Lewis acid and Lewis base properties.[67] Actually, the first example of the combination of a metal centre and a phosphine ligand which contains an additional amine functionality was already reported by

[65] T. Arai, H. Sasai, K.-I. Aoe, K. Okamura, T. Date, M. Shibasaki, *Angew. Chem.* **1996**, *108*, 103; *Angew. Chem. Int. Ed.* **1996**, *35*, 104.
[66] For reviews, see: a) M. Shibasaki, H. Sasai, T. Arai, *Angew. Chem.* **1997**, *109*, 1290; *Angew. Chem. Int. Ed.* **1997**, *36*, 1237; b) M. Shibasaki, H. Gröger in *Topics in Organometallic Chemistry Vol 2* (Ed.: S. Kobayashi), Springer, Berlin, **1999**, p. 199.
[67] a) Y. Hamashima, D. Sawada, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **1999**, *121*, 2641; b) D. Sawada, M. Shibasaki, *Angew. Chem.* **2000**, *112*, 215; *Angew. Chem. Int. Ed.* **2000**, *39*, 209; M. Kanai, Y. Hamashima, M. Shibasaki, *Tetrahedron Lett.* **2000**, *41*, 2405; d) Y. Hamashima, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2000**, *122*, 7412; e) Y. Hamashima, M. Kanai, M. Shibasaki, *Tetrahedron Lett.* **2001**, *42*, 691; f) M. Takamura, K. Funabashi, M. Kanai, M. Shibasaki, *J. Am. Chem. Soc.* **2001**, *123*, 6801; g) G. Manickam, H. Nogami, M. Kanai, H. Gröger, M. Shibasaki, *Synlett* **2001**, 617.

Hayashi.[68] The application of this metal complex gave excellent results in the asymmetric aldol reaction. Shibasaki´s complex consisted of aluminium coordinated to a BINOL-based diol, which included a phosphinoyl moiety: it represented the required Lewis base functionality. The aluminium centre behaved as a Lewis acid, activating the carbonyl group and the oxygen atom of the phosphine oxide acted as a Lewis base activating silylated nucleophiles. The efficency of the complex was examined in the synthesis of enantiomerically enriched cyanohydrines by asymmetric addition of trimethylsilylcyanide to aldehyde (Scheme 23).[67]



Scheme 23 Application of bifunctional catalysts in asymmetric cyanosilylation.

The use of tributylphosphine as an additive led to a remarkable increased enantioselectivity of up to 97% *ee*. A possible explanation of the surprising effect of the additive is depicted in Figure 7.

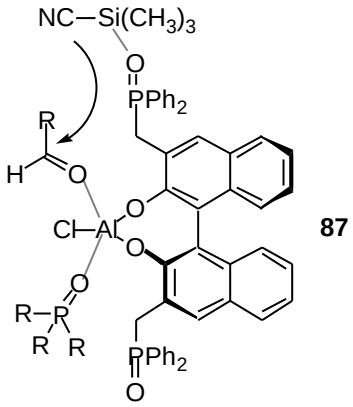


Figure 5 Mechanism of the Lewis acid/Lewis base catalysis.

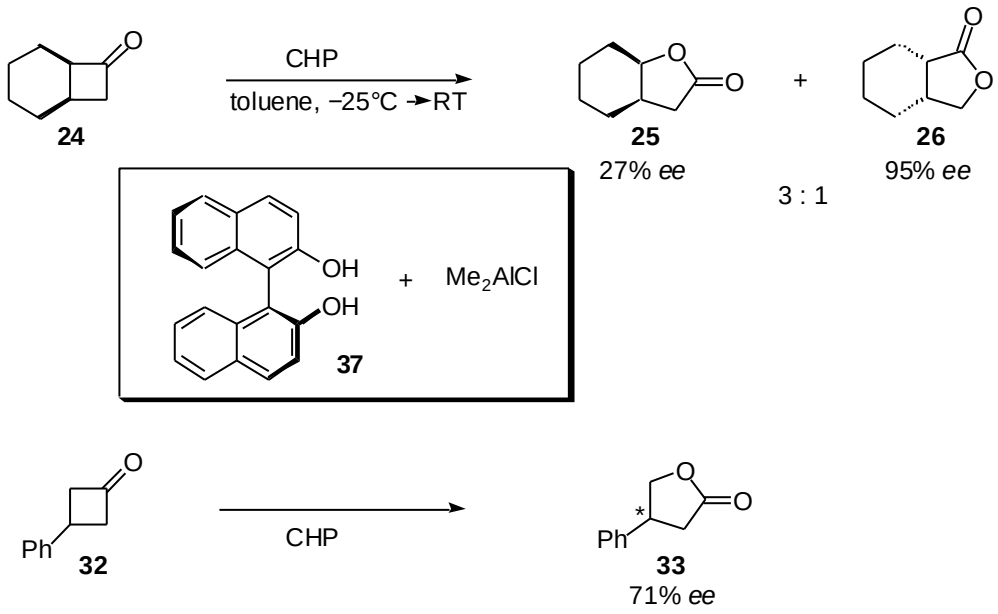
[68] Y. Ito, M. Sawamura, T. Hayashi, *J. Am. Chem. Soc.* **1986**, *108*, 6405; T. Hayashi, M. Sawamura, Y. Ito, *Tetrahedron* **1992**, *48*, 1999.

It was proposed that the aluminium centre is now pentavalent and the external phosphine oxide is bound to the metal centre. The aldehyde coordinated to the metal centre and the trimethylsilylcyanide interacting with the Lewis base part of the chiral ligand are very close to each other. The subsequent transfer of the cyanide to the aldehyde takes place in a highly enantioselective fashion. Thus, upon designing an Al-based asymmetric catalytic reaction, not only the steric substitution pattern of the ligand, but also electronic factors should be taken into account and be utilized to enhance the enantiodiscrimination. These electronic factors comprise both electron-withdrawing/donating groups attached to the ligand influencing the metal-ligand coordinative bonding and coordinating substituentes as employed by Jørgensen and Shibasaki (vide supra). The evaluation of aluminium for an asymmetric Baeyer-Villiger variant described in the following chapter was inspired by the aforementioned catalyses. These literature examples appeared to be a useful starting point, since they also involved BINOL – a ligand that proved superior to all the others tested in Al-mediated Baeyer-Villiger oxidations in the present thesis.

3.3 Aluminium-mediated asymmetric Baeyer-Villiger oxidation

All asymmetric metal-catalyzed Baeyer-Villiger reactions described so far have their basis in chirally modified transition metals. This is surprising when taking into account that for many other catalytic transformations highly successful main group element-derived catalysts are known. Therefore, it seems appropriate to extend the search for novel catalytic systems to main group metals. In particular to disclose a new access to an asymmetric Baeyer-Villiger reaction, aluminium was envisaged to be a suitable central atom as Al-complexes had already been shown to be effective in catalyses with carbonyl substrates (see chapter 3.2). An efficent asymmetric Al-system found was based on the combination of Me_2AlCl with 1 equivalent of enantiopure BINOL as chiral ligand.[69] Enantioselective oxidation of racemic bicyclic as well as prochiral monosubstituted cyclobutanones could be achieved by using an hydroperoxide as oxygen source (Scheme 24).

[69] O. Beckmann, Dissertation, RWTH, Aachen University, **2000.**

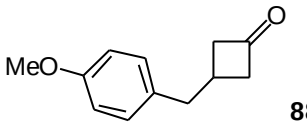
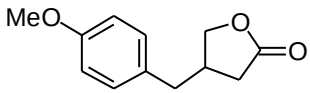
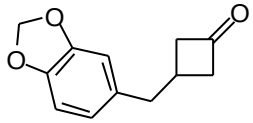
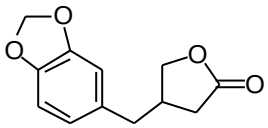
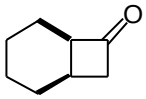
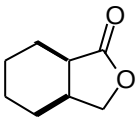
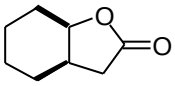
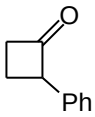
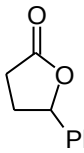
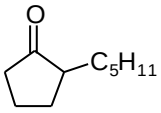
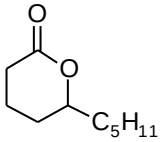


Scheme 24 Al-mediated Baeyer-Villiger oxidation.

In principle, starting from bicyclic cyclobutanones, two regioisomeric lactones could be formed depending on which side of the carbonyl group the oxygen insertion occured. This transformation represents an example of enantiodivergent reaction, since one regioisomeric enantioenriched lactone is mainly produced from one enantiomer of the starting material while the substrate antipode gives rise to the other nonracemic regioisomeric product.[41] A general observation concerning the substrates was that a wide range of cyclobutanones could be enantioselectively oxidized. This also holds true for bicyclic systems as well as prochiral monosubstituted substrates. Neither the introduction of chlorine in para position of the phenyl ring nor the replacement of a phenyl group with a alkylic or benzylic group at position C3 had a detrimental effect.[69] Moreover, some other substrates have been synthesized and used in the Al-mediated Baeyer-Villiger oxidation. As reported in Table 1, a good level of enantioselectivity was achieved in the oxidation of *p*-methoxybenzylcyclobutanone (**88**), namely 73% *ee* while the cyclobutanone bearing the pyperonyl substituent in position 3 provided a lower enantioselection (entry 2). In entry 3, the oxidation of the bicyclooctanone **24** was performed, inverting the sequence of addition of the reagents, i.e. the oxidant was now added before the substrate.[69] In comparison to the standard procedure, it should be noted that not only the conversion and enantioselectivity are lower but also by-products were formed. Racemic monosubstituted cyclobutanones are interesting starting materials as well and both 2-phenylcyclobutanone (**57**) and 2-pentylcyclopentanone (**29**) have been tested (entry 4, 5). The first one was oxidated with 33% conversion to the corresponding lactone with 23%

enantiomeric excess while the 2-substituted cyclopentanone did not undergo to oxidation at all.

Table 1 Screening of substrates.[a]

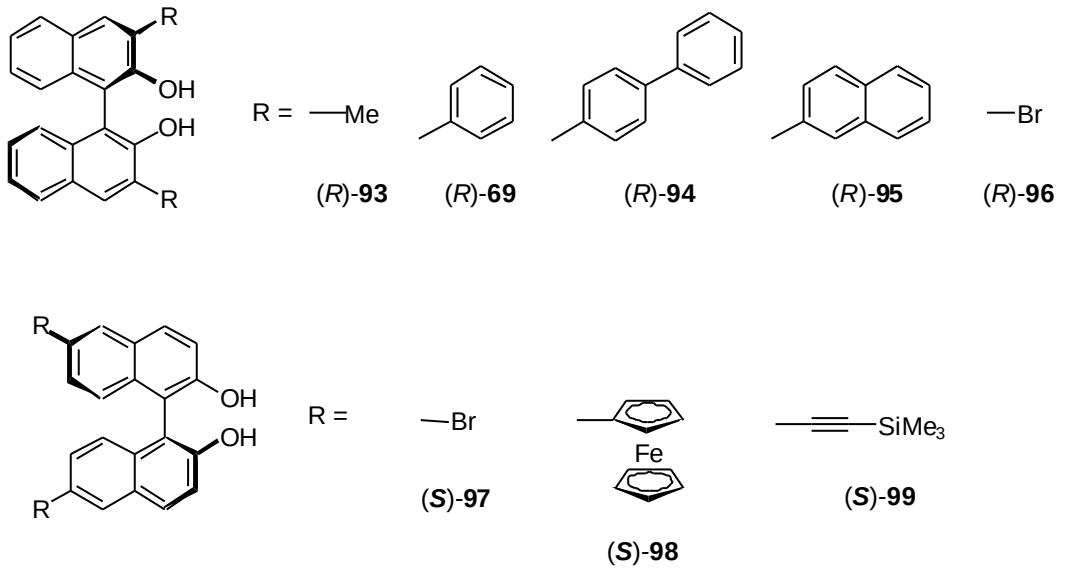
Entry	Substrate	Product	*ee* [%]
1	 **88**	 **89**	73
2	 **90**	 **91**	58
3[b]	 **24**	 **26**	48
		 **25**	41
4	 **57**	 **92**	23[c]
5	 **29**	 **30**	no conv.

[a] Reaction conditions: according to general protocol GP5, Experimental section.
[b] Inverting the order of addition of substrate and oxidant. Ratio n/ab = 6
[c] 33% conversion

Under standard conditions, 50 mol% of catalyst was used but it was observed that it was possible to reduce the catalyst loading to 15 mol% upon which the *ee* just dropped down to 68%, the isolated yield being still higher than 80%.[69]

3.3.1 Influence of the substitution pattern

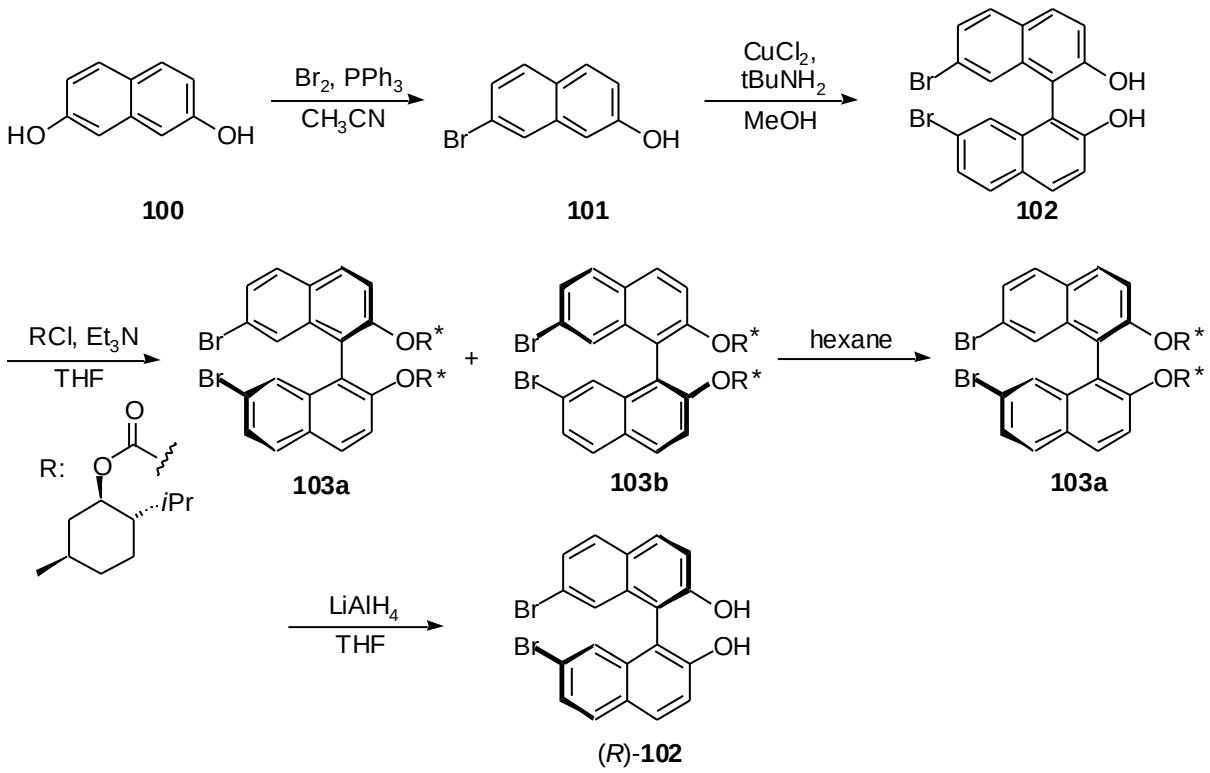
A survey of various chiral diols as ligands revealed the binaphthyl scaffold to be the most effective one in transferring asymmetry.[69] In order to investigate the stereoelectronic factors influencing the course of the reaction, a series of ligands was prepared that would make it possible to distinguish between the steric effects of the ligand side chains and their possible electronic role. Bulky substituents in the ortho position are often reported in the literature as essential in order to improve enantioselectivity.[70] Therefore, several BINOL derivatives were synthesized. A first class of BINOL compounds included various substituents in the ortho position, close to the binding site of the ligand to the metal. They were prepared according to the synthetic strategy developed by Pu and co-workers.[71] The central step in this synthesis is the formation of the bond between BINOL and the substituent R in a Suzuki coupling reaction.[72] Also 6,6'-substitutions in BINOL were possible by means of Suzuki coupling reactions but alternatively by Sonogashira coupling as well.



Scheme 25 Various substituted BINOLs.

[70] a) K. Maruoka, T. Itoh, T. Shiarasaka, H. Yamamoto, *J. Am. Chem. Soc.* **1988**, *110*, 310; b) K. Maruoka, Y. Hoshino, T. Shiarasaka, H. Yamamoto *Tetrahedron Lett.* **1988**, *29*, 3967; c) T. R. Kelly, A. Whiting, N. S. Chandrakumar, *J. Am. Chem. Soc.* **1986**, *108*, 3510; d) C. Chapuis, J. Jurczak, *Helv. Chim. Acta* **1987**, *70*, 436.
[71] a) W.-S. Huang, Q.-S. Hu, L. Pu, *J. Org. Chem.* **1998**, *63*, 1364; b) K. S. Simonsen, K. V. Gothev, K. A. Jørgensen, *J. Org. Chem*. **1998**, *63*, 7536.
[72] a) Suzuki, *Acc. Chem. Res.* **1982**, *15*, 178; b) M. Sharp, W. Cheng, V. Snieckus, *Tetrahedron Lett.* **1987**, *28*, 5093.

A further substitution site to consider was position 7,7'. Even if many 3, 3'- and 6, 6'-disubstituted BINOL derivatives have been reported, only few 7,7'-disubstituted 2,2'-dihydroxy-1,1'binaphthyls have been synthesized in optically active form. Such compounds cannot be obtained by simple derivatization of enantiopure BINOL. A suitable procedure for the synthesis was reported by Umani-Ronchi et al.[73] 2,7-Dihydroxynaphthalene (**100**) was converted into 7-bromo-2-hydroxynaphthalene **101** which, in turn, was subjected to oxidative coupling leading to the desired racemic compound **102**. The resolution was carried out according to the general procedure introduced by De Lucchi: the BINOL derivative was treated with (1*R*,2*S*,5*R*)-(–)-menthyl chloroformate in the presence of triethylamine, and the resulting diastereomeric mixture of the bis(menthyl) carbonates could be resolved by crystallization. Reduction of the diastereomer by an excess of $LiAlH_4$ afforded the enantiopure bromo BINOL derivative (*R*)-**102**.



Scheme 26 Synthesis of optically active (*R*)-**102**.

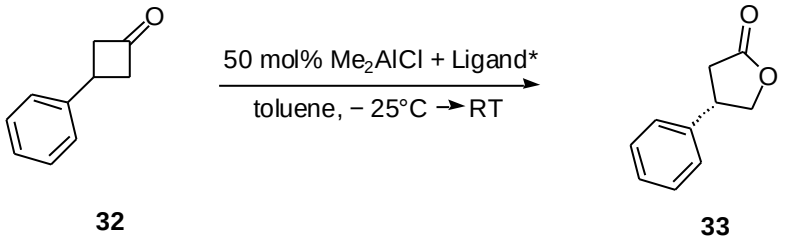
[73] M. Bandin, S. Casolari, P. G. Cozzi, G. Proni, E. Schmohel, G. P. Spada, E. Tagliavini, A. Umani-Ronchi, *Eur. J. Org. Chem.* **2000**, 491.

For the use in the metal-mediated Baeyer-Villiger reaction, BINOL **102** was synthesized according to the aforementioned literature as were the 3,3'- and 6,6'-disubstituted BINOL compounds.

Many 3,3'-disubstituted BINOLs tested in the Baeyer-Villiger oxidation merely led to racemic lactones if they allowed full conversion at all. Introduction of a methyl or a phenyl group in the ortho position caused a decrease of enantioselectivity in the oxidation of 3-phenyl cyclobutanone (**32**) from 71% to 40% and 6% *ee* respectively (entries 1 and 2, Table 2). More sterically demanding substituents, such as biphenyl and naphthyl, led to racemic products if they did not prevent the conversion to be completed. Yet, incorporation of bromine at the 6- and 6'-position of BINOL, rather remote from the coordinated metal, was shown to increase enantioselectivity to 77% *ee* in the oxidation of 3-phenylcyclobutanone (**32**) (entry 6). Introduction of a substituent in that position seemed to have an influence on enantioselectivity,[74] which may be attributed to the electron-withdrawing effect of bromine on the oxygen. With Me_3Si-acetylenyl in the same position, even a higher *ee* of 81% could be attained under the very same reaction conditions. This result seems to ascertain the above-mentioned assumption that the electron-withdrawing properties of the substitent account for the increase of enantioselection. Moreover, a peculiarity of this protected ethyne moiety is that it contains a labile protecting group, which could be cleaved upon addition of the acidic Me_2AlCl precursor. Another possibility could be that HCl released by the formation of the Al-BINOL complex would lead to the deprotection. However, the chlorine presumably remains attached to the Al as shown by replacement of it with cyano- or ethoxy-group (vide infra). Thus, it would be worthwhile to repeat this experiment with an analoguous BINOL ligand, that bears a more stable silyl group or an alkyl group on the alkyne, thereby excluding the ambiguous reaction possibilities.

[74] a) H. Sasai, T. Tokunaga, S. Watanabe, T. Suzuki, N. Itoh, M. Shibasaki, *J. Org. Chem*. **1995**, *60*, 7388; b) M. Terada, Y. Motoyama, K. Mikami, *Tetrahedron Lett.* **1994**, *36*, 6693; c) C. Qian, T. Huang, *Tetrahedron Lett.* **1997**, *38*, 6721; d) C. T. Qian, T. S. Huang, C. J. Zhu, J. Sun, *J. Chem. Soc., Perkin Trans. 1* **1998**, 2097; e) R. Chen, C. Qian, J. G. de Vries, *Tetrahedron Lett.* **2001**, *42*, 6919.

Table 2 Effect of substitution on the binaphthyl scaffold in the oxidation of 3-phenlcyclobutanone (**32**).[a]



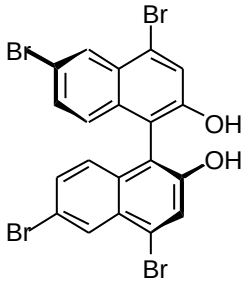
32 **33**

Entry	Ligand	Conv. %	*ee* %
1	(*R*)-**93**	100	40
2	(*R*)-**69**	100	6
3	(*R*)-**94**	72	rac
4	(*R*)-**95**	65	rac
5	(*R*)-**96**	100	rac
6	(*S*)-**97**	100	77
7	(*S*)-**98**	100	66
8	(*S*)-**99**	100	81
9	(*R*)-**102**	100	64

[a] Reaction conditions: according to general protocol GP5, Experimental section.

The higher enantioselectivity may be attributed to the electron withdrawing effect of bromine on the oxygen. Therefore, further modification of the binaphthol scaffold introducing the same substituent in position 7 and 7' were undertaken. In that case there was not only an electronic effect but also the rotation angle between the two naphthyl moiety would be affected. 7,7'-Disubstituted BINOL **102** was tested in the aluminium-mediated oxidation of 3-phenyl cyclobutanone (**32**) in toluene and with CHP as oxidant. As result, full conversion to the corresponding lactone and 64% enantiomeric excess were achieved (enty 9).

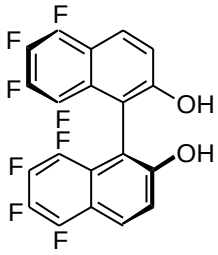
The outcome was different when one employed the tetrasubstituted BINOL (*S*)-**104** depicted in Figure 6, which was synthesized by bromination of protected BINOL in acetic acid.[75] As opposed to the 6,6'-dibromo BINOL (**97**), the additional bromine substitutents in positions 4 and 4' had the effect to prevent enantioselection.



(*S*)-**104**

Figure 6 (*S*)-4,4',6,6'-Tetrabromo-2,2'-hydroxy-1,1'-binaphthyl.

Yudin et al. recently reported the synthesis and catalytic applications of fluorinated BINOL derivatives, an isoestere of BINOL with modulated coordination preferences.[76] The substitution of fluorines at the 5,5',6,6',7,7',8 and 8' positions of BINOL was considered to induce a considerable electronic perturbation of the aromatic system.



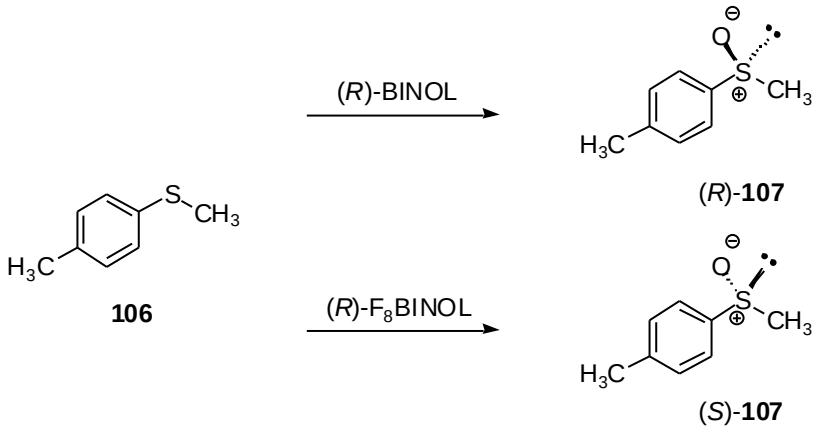
105

Figure 7 (*S*)-F_8-BINOL.

A comparison of the electrostatic potential surfaces (calculated on the basis of AM1) revealed a noticeable difference in the distribution of electron density. The electron-deficient nature of the aromatic rings raises the oxidative stability of the flourinated derivative in comparison to BINOL as well as increases the acidity of the ring-bound hydroxy groups by a factor of 10. Moreover, it was found by X-ray analysis that the torsion angle between the two

[75] L.Z. Gong, Q.S. Hu, L. Pu *J. Org. Chem*. **2001**, 66, 2358.
[76] A. K. Yudin, L. J. M. Martyn, S. Pandiaraju, J. Zheng, A. Lough, *Org. Lett.* **2000**, *2*, 41.

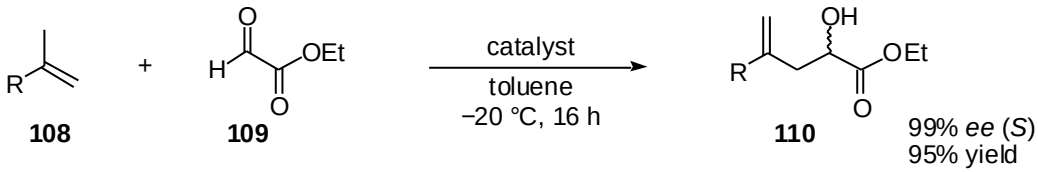
tetrafluoronaphthol moieties was only 1.4° larger then in the unsubstituted BINOL. Thus, the fluorination appears to have a fairly insignificant steric influence on the torsion angle. This was actually expected, since the size of the fluorine atom is very similar to hydrogen. In studying the catalytic potential of F_8-BINOL, Yudin and co-workers found something unusual. In the sulfide oxidation with titanium(IV), the (*R*)-sulfoxide was formed in excess in the presence of (*R*)-BINOL, whereas the (*S*)-product predominated when (*R*)-F_8-BINOL was used (Scheme 27).[77] Interestingly they found by structural studies on the titanium complex that instead of chelating to one metal centre as BINOL, the fluorinated derivative bridged two metal centres.



Scheme 27 Comparison between the BINOL and F_8-BINOL in the Ti-catalyzed asymmetric oxidation of a sulfide.

In asymmetric ene-reactions, even better results were achieved when a pseudoracemic mixture of (*R*)-BINOL and (*R*)-F_8-BINOL in combination with titanium was used. In the presence of this mixture, titanium took up one molecule of each, producing a pseudoracemic catalyst,[78] which, in the reaction between ethyl glyoxylate **109** and aliphatic olefins **108,** led to the desired α–hydroxyester with 99% *ee* (Scheme 28).

[77] a) Y. Chen, S. Yekta, L. J. P. Martyn, J. Zheng, A. K. Yudin, *Org. Lett.* **2000**, *2*, 3433; b) L. J. P. Martyn, S. Pandiaraju, A. K. Yudin, *J. Organomet. Chem.* **2000**, *603*, 98.
[78] S. Pandiaraju, G. Chen, A. Lough, A. K. Yudin, *J. Am. Chem. Soc.* **2001**, *123*, 3850.



108 **109** **110**

Catalyst: (*R*)-BINOL (5 mol%), (*S*)-F_8BINOL (5 mol%), Ti(O*i*Pr)$_4$ (5 mol%)

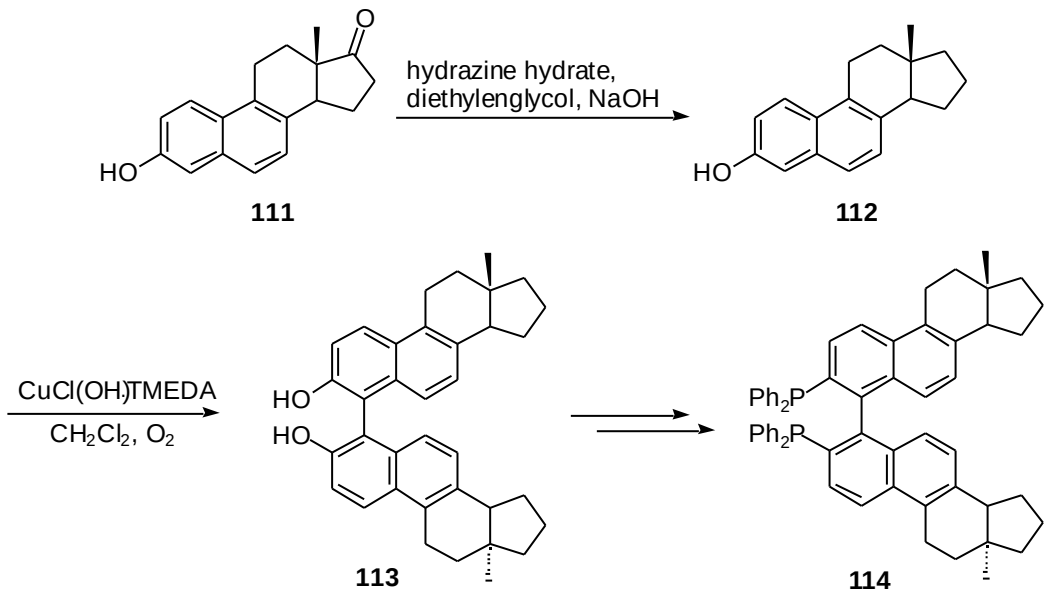
Scheme 28 Use of a catalyst derived from a mixture of (*S*)-F_8-BINOL and (*R*)-BINOL in the glyoxylate-ene reaction.

Since the best result obtained in Al-mediated Baeyer-Villiger oxidation was achieved with bromine in position 6,6' of BINOL, one envisaged that fluorinated BINOL could have a similar effect. Therefore, (*S*)-F_8-BINOL was employed in a test reaction, i.e. the Baeyer-Villiger oxidation of 3-phenylcyclobutanone under the standard conditions used for all the Al catalyses.[79,80] As expected, the presence of the fluorine had an influence, but not a positive one. Unfortunately, the conversion of the oxidation reaction was not complete and only 23% *ee* was achieved.

3.3.2 Aluminium-mediated Baeyer-Villiger oxidation with steroidal ligands

In order to synthesize atropoisomeric ligands, such as BINOL derivatives, a resolution of a racemic intermediate or the final product is required. Using a steroid as precursor, one can take advantage of the steroid local central chirality for the separation of the ligands. The diastereomeric ligands will then behave in catalysis as two pseudo-enantiomers due to the mirror image stereochemistry of the axis, i.e., due to the axial chirality. BINOL and BINAP analogues that were derived from a steroid, such as equilenine **111**, have found application as ligands in asymmetric catalysis.[81] For the synthesis of **113** and **114**, equilenine **111** was deoxygenated to desoxy-equilenine **112** which was then coupled with 96% yield using Koga´s copper catalyst at 0° C. At this temperature, a diastereomeric ratio of 1:1.5 was obtained, and the mixture of the two diastereomers could be easily separated by column chromatography (Scheme 29).

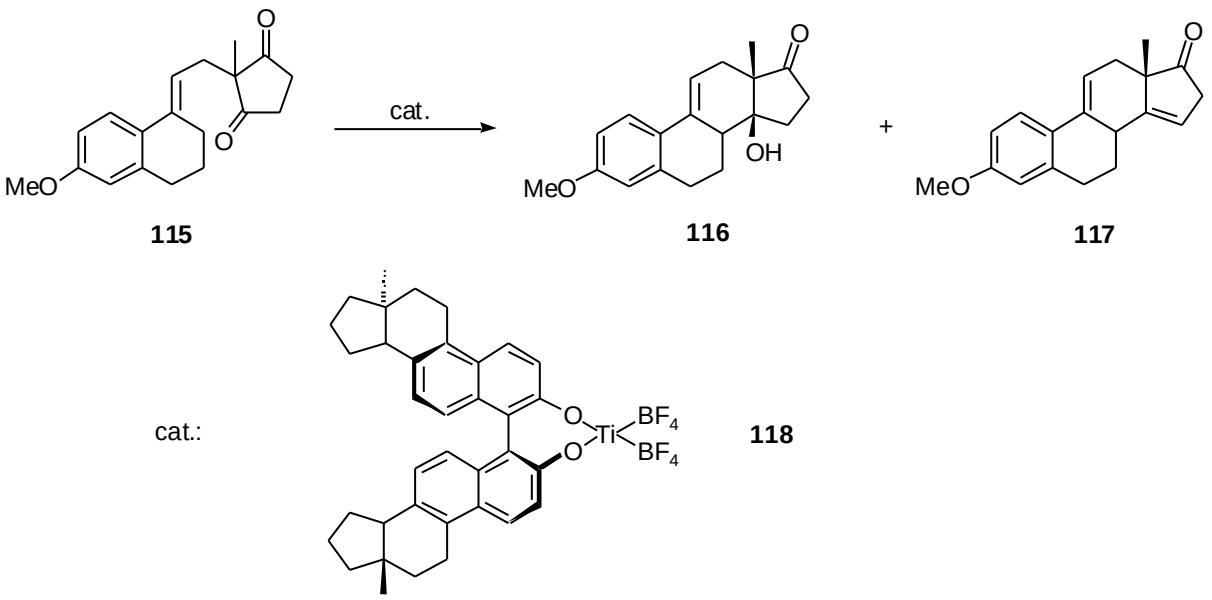
[79] Enantiopure (*S*)-F_8-BINOL was kindly provided by Professor Dr. A. Yudin, University of Toronto, Canada.
[80] Standard conditions according to general procedure GP5, Experimental section.
[81] a) V. Enev, C. L. J. Ewers, M. Harre, K. Nickisch, J. T. Mohr, *J. Org. Chem.* **1997**, *62*, 7092; b) V. Enev, M. Harre, K. Nickisch, M. Schneider, J. T. Mohr, *Tetrahedron: Asymmetry* **2000**, *11*, 1767.



Scheme 29 Synthesis of bis-steroidal phosphine **114**.

BINOL derivative **113** was initially used in the Noyori-type asymmetric reduction of acetophenone with $LiAlH_4$, in EtOH.[82] Enantiomeric excesses up to 92.8% were achieved in the synthesis of (*R*)-phenylethanol with (*R*)-**113** at – 70°C. In order to see if both ligands behaved as enantiomers, diphosphine **114** was synthesized and applied in the asymmetric hydrogenation of methyl acetoacetate with $RuCl_2$-(ligand)(DMF). No difference concerning the asymmetric induction between the two diastereomers (R_{ax})-**114** and (S_{ax})-**114** was observed. The BINOL-steroid-derivative was also used as ligand in the Lewis acid mediated asymmetric ene cyclization (Scheme 30). The (R_{ax})-bis-steroid titanium complex (R_{ax})-**118** was found to afford a good level of enantiocontrol, viz 72% yield and 70% *ee*. Interestingly, with the complex derived from the other diastereomer [(S_{ax})-one], the other enantiomer was achieved, but with moderate enantioselectivity, namely 54% *ee* only. Thus, for the first time a remarkable difference between the two diastereomeric ligands was observed. In this case, the steroid-derived ligands proved to be superior to BINOL which indicated that the chirality on the backbone had a prevailing influence.

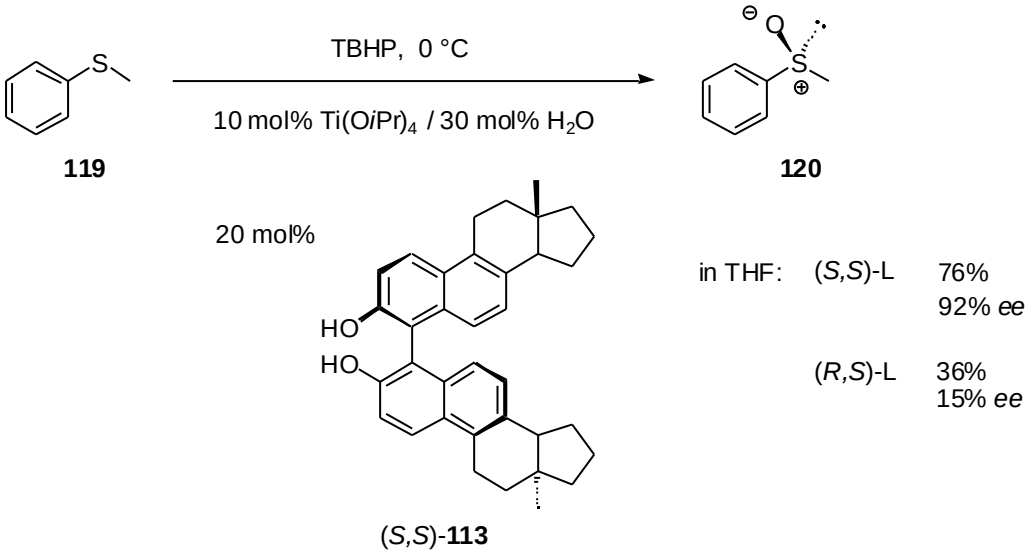
[82] R. Noyori, I. Tomino, Y. Tanimoto, M. Nishizawa, *J. Am. Chem. Soc.* **1984**, *106*, 6709.



Scheme 30 BINOL-steroid-titanium complex as catalyst in the asymmetric ene cyclization.

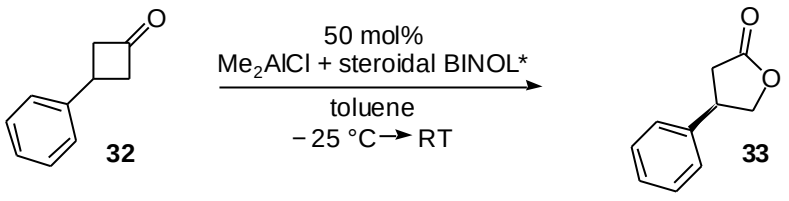
The same effect, but amplified, was reported by Bolm and Dabard using the same bis-steroidal binaphthyl ligand in the catalytic asymmetric oxidation of sulfides to sulfoxides (Scheme 31).[83] They used Uemura´s system (BINOL/Ti(O*i*Pr)$_4$) as they investigated the effect of chirality of the backbone of the binaphthyl scaffold on enantioselectivity. Indeed, the bissteroidal ligands proved to be superior over BINOL and both activity and enantioselectivity were dependent on which diastereomer was used. In the oxidation of methyl phenyl sulfide (**119**) with TBHP (70% in water) in the presence of 10 mol % of titanium catalyst (ratio Ti:ligand = 1:2), 76% yield and 92% *ee* were obtained with the (*S*,*S*)-ligand compared to 36% yield and 15% *ee* with the (*R*,*S*)-diastereomer.

[83] C. Bolm, O. Dabard, *Synlett* **1999**, *3*, 360.



Scheme 31 Titanium-catalyzed oxidation of sulfides using steroidal derived BINOL ligands.

As the substituents on the binaphthyl scaffold were previously found to have an influence on the enantioselectivity of the product in Baeyer-Villiger oxidations (see 3.3.1 influence of the substitution pattern), such diastereomeric steroid-derived ligands appeared interesting in that the substituents on the binaphthyl scaffold, here, imparted central chirality. Thus, not only the sheer steric demand of the substituents could have an effect on the enantioselectivity, but also the additional chirality besides the axial chirality of BINOL. The question to address was whether the central chirality would add or oppose to the axial asymmetry of the BINOL backbone as to the enantiodiscrimination during the oxidation process. To this end, six different steroidal BINOL ligands **121-126** were tested in the aluminium-mediated oxidation of 3-phenylcyclobutanone (Scheme 32).

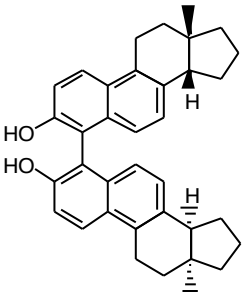
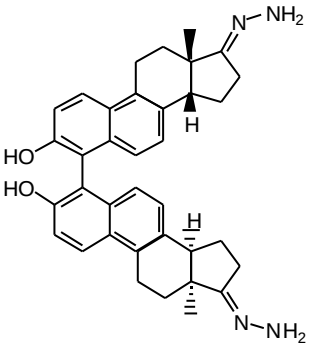
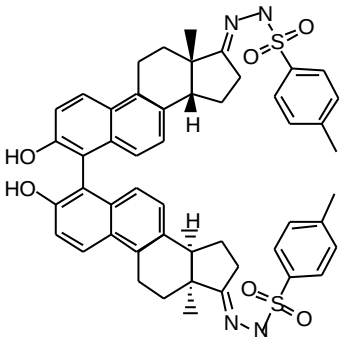


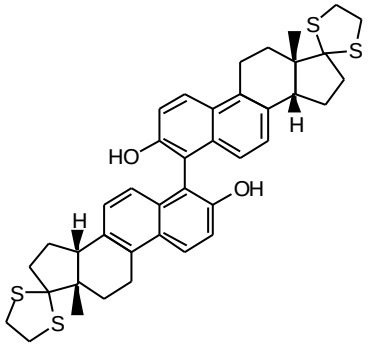
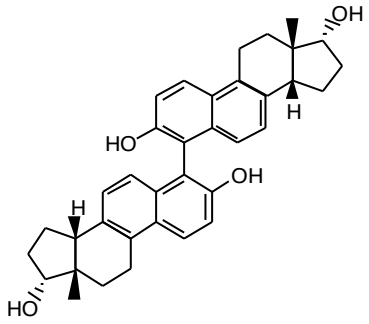
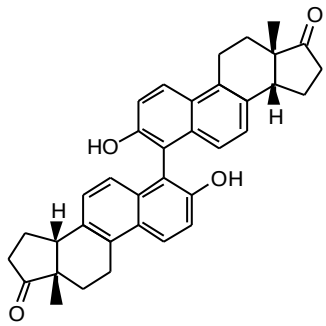
Scheme 32 Baeyer-Villiger oxidation of 3-phenylcyclobutanone using an Al catalyst derived from steroidal BINOL ligands.

The six BINOL ligands **121-126** differed in the substitution of the steroid part (Table 3). It was found that in all cases the chirality of the binaphthyl axis determined the direction of the

enantioselectivity of the product, i.e. the (R_a)-diastereomer (or (*R*)-pseudoenantiomer) of each steroid ligand led to the (−)-lactone whereas the use of the (S_a)-diastereomer (or (*S*)-pseudoenantiomer) resulted in the (+)-lactone. Furthermore, the central chirality influenced the enantiomeric excess of the product to a minor extent only since the *ee*-values obtained with each pair of diastereomers were almost the same. For instance, (S_a)-**121** led to (+)-**33** with 67% *ee* while (R_a)-**121** produced (−)-**33** with 68% *ee*. However, the electronic properties of the substituents in ligands **121**-**126**, seemed to have an impact on the reaction.

Table 3 Steroidal ligands tested in the Al-mediated Baeyer-Villiger oxidation.[a]

Entry	L	Ligand	Configuration	Conversion [%] *ee* [%]	Product
1	**121**		(S_a)	100 67	(+)
2			(R_a)	100 68	(–)
3	**122**		(S_a)	60 8	(+)
4			(R_a)	40 rac	
5	**123**		(R_a)	100 67	(–)

Entry	L	Ligand	Configuration	Conversion [%] *ee* [%]	Product
6	**124**		(S_a)	100 60	(+)
7			(R_a)	100 68	(–)
8	**125**		(S_a)	100 69	(+)
9			(R_a)	100 69	(–)
10	**126**		(R_a)	100 72.5	(–)

a. For details of the reaction see general protocol GP5, Experimental Section.

The presence of a hydrazone group as in **122** inhibited the oxidation, probably due to the free amino nitrogen, a phenomenon which was already observed with free amine additives in this transformation.[69] With a tosyl hydrazone group as in **123**, however, this detrimental effect of nitrogen was not evident because here it was no longer basic. The other ligands **121** and **124-126** virtually brought about the same *ee* values for the lactones, indicating that the oxidation was fairly unsusceptible to variations from thiolane or alcohol groups over carbonyl functionalities in simple alkyl structures. It should be noted that many of these steroid compounds were not entirely soluble in toluene. For this reason, some of it remained inaccessable for coordination with aluminium. As a result, achiral metal species could have been involved in the catalysis as well, leading to a reduced enantioselection.

3.3.3 Modification of the system and structure of the complex

In concert with various aluminium precursors, BINOL forms highly enantioselective catalysts that have been employed in many asymmetric processes. Despite the importance of Al-BINOL complexes, however, there is little information regarding the structure of these species. Investigations into the structure of chiral aluminium complexes were performed by means of cryoscopic analysis, which led to the conclusion that complexes of aluminium with BINOL that bore bulky substituents in ortho position were monomeric.[84] Solid state structures of aluminium complexes with chiral ligands, especially aminoacids, have been determined by Olivier et al.[85] The reaction between trialkylaluminium and ephedrine formed dimeric complexes with an Al_2O_2 central ring and a coordinative Al-N bond. Dimeric complexes are also formed by the combination of trialkylaluminium and monoalcohols such as menthol.[86] Here, aluminium is tetrahedrically coordinated. In many cases, it was found that monomeric, dimeric and oligomeric species are in equilibrium in solution.[87] Crystals of these complexes have been obtained only when in the ligand a nitrogen or sulfur is present in addition to an hydroxy group. In order to characterize such complexes, ^{27}Al-NMR had been useful: in organoaluminium compounds, the chemical shift δ (^{27}Al) is an indicator for the coordination number of the aluminium atom. For instance, in a monomeric compound R_3Al with three-fold coordinated aluminium atoms, the chemical shift δ (^{27}Al) lies between 280 and 210 ppm, whereas for four-coordinated aluminium in $(R_nAlX_{3-n})_m$ complexes δ (^{27}Al) is between 180 and 125 ppm. In organoaluminium compounds with five-coordinated Al atoms δ (^{27}Al) was found between 125 and 100 ppm. Aluminium complexes such as $R_{3-n}AlX_n$ are coordinatively and electronically insaturated and, therefore, it is possible to obtain higher valence numbers as well as coordination. As a consequence of their Lewis acidity, they react with a Lewis base to form neutral donor-acceptor complexes or they build dimers, trimers or even polymers through autoassociation. If the X substituent contains at least a free electron pair, the association will occur by means of a donor bond of bridged atoms. Moreover, the different aggregated species can exist in equilibrium to each other. Bulky rests on the aluminium have a detrimental effect to aggregation. When BINOL and aluminium are mixed in a ratio 1:1, different structures are possible, which are depicted with their chemical shift in the ^{27}Al NMR.

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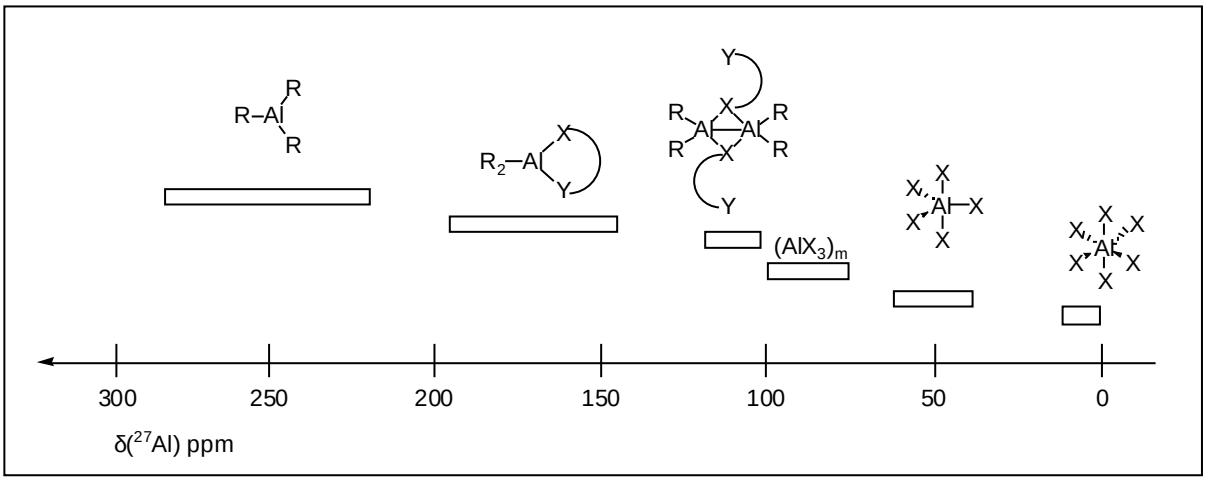
[84] K. Maruoka, T. Itho, T. Shirasaka, H. Yamamoto, *J. Am. Chem. Soc.* **1988**, *110*, 310.
[85] M. L. Sierra, V. S. J. de Mel, J. P. Olivier, *Organometallics* **1989**, *8*, 2486.
[86] M. L. Sierra, R. Kumar, V. S. J. de Mel, J. P. Oliver, *Organometallics* **1992**, *11*, 206.
[87] a) J. P. Olivier, R. Kumar, *Tetrahedron* **1990**, *9*, 409; b) S. Pasynkiewicz, W. Ziemkowska, *J. Organomet. Chem.* **1992**, *437*, 99.

The stucture of the aluminium chiral complex is strongly dependent on which metal precursor has been used.[88]



Scheme 33 The chemical shift δ (^{27}Al) as indicator for the coordination number of the aluminium atom.

The fact that multiple structural options were conceivable for aluminium complexes proved to be important for Baeyer-Villiger oxidations involving aluminium.

During the evaluation of new Al-based Baeyer-Villiger systems, various metal sources were tested. However, among the precursors $EtAlCl_2$, $AlCl_3$ and $Al(OtBu)_3$ none could, in combination with BINOL, ensure complete oxidation to lactones, let alone with enantioselectivity;[69] Me_3Al with BINOL allowed full conversion, but failed to produce at least modest *ee*s. Solely dialkyl aluminium chlorides, Me_2AlCl or Et_2AlCl, were successful and of these, the dimethyl one gave somewhat higher *ee*s than the diethyl metal halide. It was not possible to find a correlation between the Lewis acidity of the metal precursor and the activity of the corresponding complexes with BINOL. The scale of activity in the order: Et_3Al < Et_2AlCl < $EtAlCl_2$ < $AlCl_3$ did not correspond with the results in the catalysis since $AlCl_3$ or $EtAlCl_2$ prevented oxidation.[69] The attempts to improve the results further were based on the system Me_2AlCl/BINOL. Substitution of chlorine with an ethoxy- or cyano-group had only a detrimental effect to the catalysis, leading to a racemic product. This was the first hint to assume that oligomeric Al species were involved in this oxidation: from the fact that Me_2AlCl gave higher *ee* values that Et_2AlCl one could infer an alkyl group (Me and Et, respectively) was still bound to the active Al centre, thereby influencing the enantiodiscrimination. On the

[88] Melanie Brunner, Dissertation, RWTH, Aachen University, **1995**.

other hand, the nature of the electronegative substituent on Al, i.e. chloro, ethoxy or cyano, was also found to affect the reaction (entries 1 and 2, Table 4). However, with both the electronegative substituent and an alkyl group still attached to the metal a monomeric BINOL-Al complex imparting enantiomeric excess on the product lactone can not be conceived. Thus, a more complex, polynuclear Al species appears to be formed during the reaction.

Table 4[a]

Entry	Metal precursor	Ligand	Additive[b]	Conv. %	*ee* %
1	Et_2AlCN	(*S*)-BINOL	-	100	*rac*
2	Et_2AlOEt	(*S*)-BINOL	-	100	*rac*
3	Me_2AlCl	0.5 equiv. (*S*)-BINOL+ 0.5 equiv. BIPOL	-	100	61
4	Me_2AlCl	(*S*)-BINOL	1 equiv. KOBu	100	31
5	Me_2AlCl	(*S*)-BINOL	1 equiv. BuLi	100	64
6	Me_2AlCl	(*S*)-BINOL	2 equiv. BuLi	100	9
7	Me_2GaCl	(*S*)-BINOL	-	60	*rac*
8	Me_2InCl	(*S*)-BINOL	-	100	*rac*

[a] Reaction conditions: according to general protocol GP5, Experimental section.
[b] equivalent with respect to BINOL.

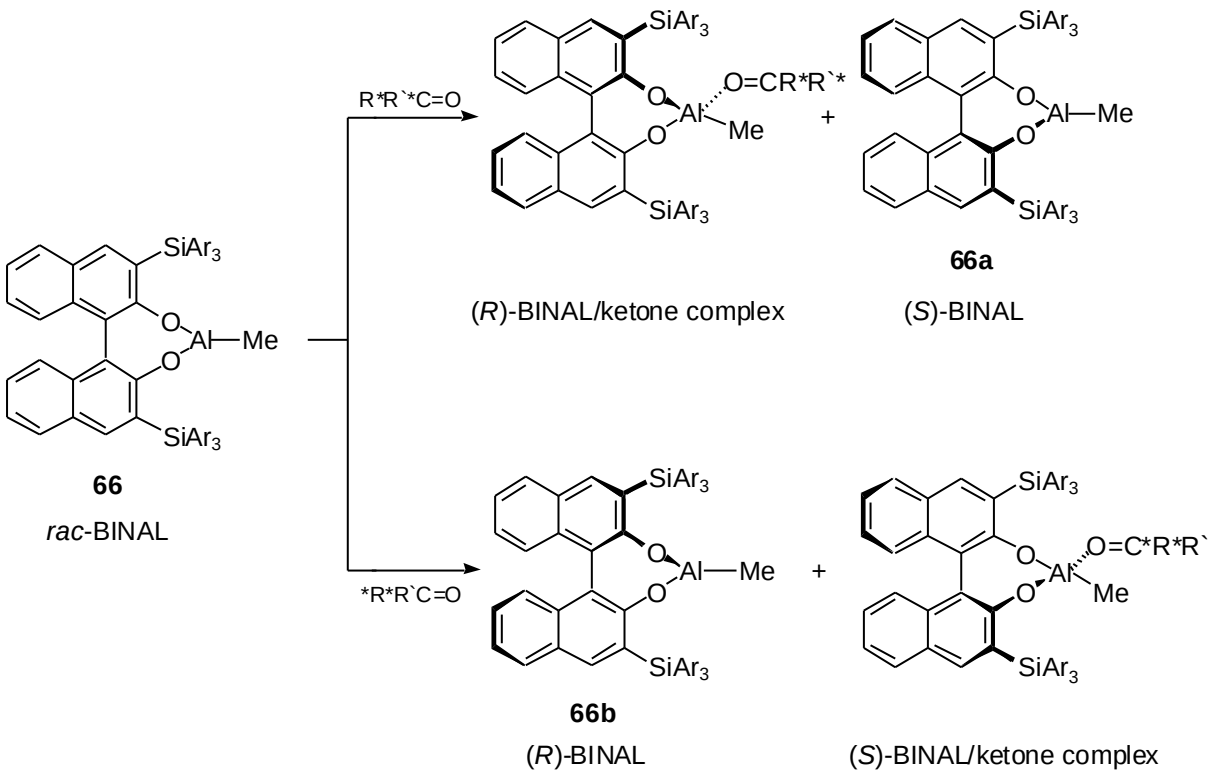
Another modification tried was the use of cumene lithium peroxide instead of the hydroperoxide. The complex was made react with the cumene lithium peroxide, which, in turn, was formed by reaction of cumene hydroperoxide with butyl lithium. This should lead to elimination (precipitation) of LiCl and formation of a BINOLate-aluminium-peroxide complex. The activity of this compound was tested in the oxidation of 3-phenylcyclobutanone. However, the corresponding lactone was formed in racemic form only.

A further variation was to exchange the aluminium centre with another metal of the group 13, such as gallium or indium. Their electronic configuration being the same, the different properties of these homologues such as atomic radii might introduce a slight and perhaps beneficial modification of the active species. One could envisage that with the heavier metals,

e.g., a modulated Lewis acidity would slow down the reaction and thereby increase the enantioselectivity. In order to keep the conditions comparable, the structurally analogous metal precursors of the Al compound were applied in the Baeyer-Villiger oxidation of 3-phenylcyclobutanone according to the general procedure GP5 (entry 7, 8).[89] The preforming time of the catalyst was the same as for aluminium but in this case racemic products were obtained. These results were believed to result from the difficulty of the Ga and In precursors to react with the hydroxy groups of BINOL under elimination of methane. Therefore, the catalytic species were formed at reflux for 3 h in toluene. Under these conditions the expected reaction should proceed smoothly. Unfortunately, again racemic butyrolactones were obtained. An explanation of these results is that there is no strong interaction between Ga or In and BINOL because of the softness of either metal in comparison to aluminium.

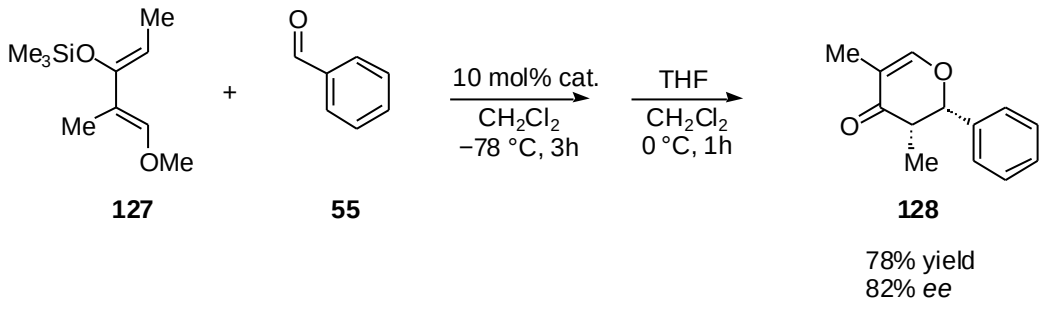
Furthermore, an attempt was undertaken to generate a nonracemic aluminium complex starting from racemic BINOL, thereby avoiding the necessity to resolve the BINOL enantiomers beforehand. This interesting method for the preparation of chiral aluminium reagents had already been reported in 1989 by Maruoka and Yamamoto. The chiral organoaluminium reagent, (*R*)-BINAL or (*S*)-BINAL could be formed in situ from the corresponding racemate by diastereoselective complexation with certain naturally occuring chiral ketones.[90] Among several terpene-derived chiral ketones, 3-bromo-camphor was found to be the most satisfactory (Scheme 34).

[89] Me_2GaCl and Me_2InCl were kindly provided by Prof. Dr. Neumüller, Philipps University, Marburg.
[90] K. Maruoka, H. Yamamoto, *J. Am. Chem. Soc.* **1989**, *111*, 789.



Scheme 34 Generation of a nonracemic aluminium complex starting from racemic BINOL.

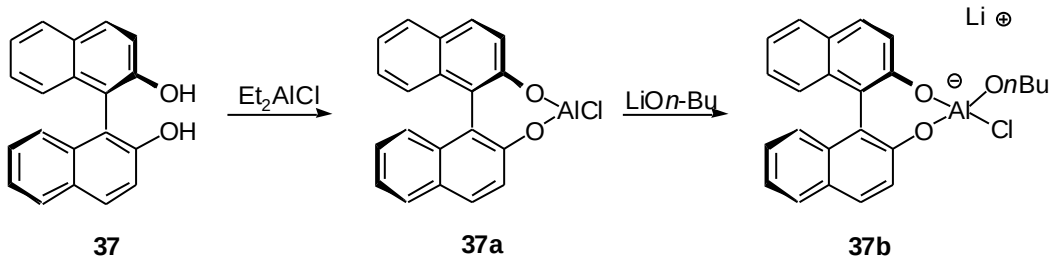
The hetero Diels-Alder reaction of benzaldehyde (**55**) and 2-methyl-1-methoxy-3-trimethylsiloxy-1,3-pentadiene (**127**) with 0.1 equiv. of racemic BINAL **66** and d-bromo-camphor at –78 °C gave rise to the *cis*-adduct as the major product with 82% *ee* (Scheme 35).



Scheme 35 Hetero-Diels-Alder reaction catalyzed by racemic BINAL **66** and d-bromo-camphor.

A transfer of this concept to the aluminium-mediated Baeyer-Villiger oxidation was tried. However, the situation here was apparently rather different: the chiral ketone seemed to compete with the substrate for oxidation. In fact only a small amount of racemic γ-butyrolactone **32** was detected by GC.

Stoichiometric amounts of chiral chloro aluminate complexes had been shown to be efficient reagents for the ring opening of meso epoxides giving optically active β-chloroalcohols.[91] Examples had been reported with menthol or BINOL aluminium complexes. Several bases for generating the aluminates were screened including primary and tertiary alkyllithiums. With BINOL the best result was observed for the lithium *n*-butoxide adduct **37b** of the aluminium BINOL derivative **37a**.



37 **37a** **37b**

Scheme 36 Synthesis of BINOL-aluminate.

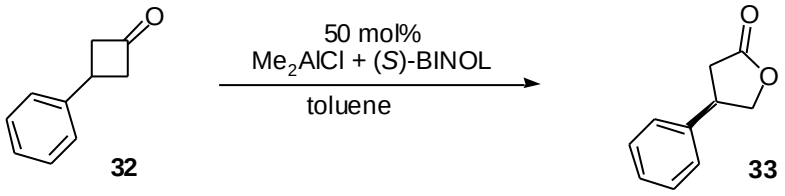
Analogously, a BINOL-Al complex derived from dimethylaluminium chloride and the enantiopure ligand was treated with KO^{t}Bu and *n*-BuLi, respectively (entry 4,5,6). However the treatment with such a strong base decreased the *ee*. Therefore the involvement of a base did not seem to imanate a more effctive complex.

3.3.4 Influence of temperature

The interest was to investigate whether the temperature had an influence on the enantioselectivity: the reaction was usually carried out without strict temperature control, starting from – 25 °C and allowed to warm to room temperature. However, by conducting the reaction in a cryostate at low temperatures, it was possible to observe some improvement in the enantioselectivity (Table 5).

[91] a) Y. Naruse, T. Esaki,H. Yamamoto, *Tetrahedron* **1988**, *44*, 4747; b) E. N. Jacobsen, F. Nakiuchi, R. G. Konsler, J. F. Larrow, M. Tokunaga, *Tetrahedron Lett.* **1997**, *38*, 773.

Table 5 Effect of the temperature.[a]



Entry	Temperature [°C]	*ee* [%]
1	+ 8	60
2	– 25	70
3	– 40	68
4	– 60	82
5	– 70	82

[a] Reaction conditions: according to general protocol GP5, Experimental section.

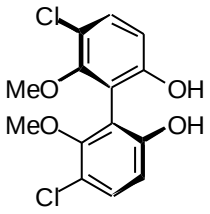
Indeed, at a constant temperature of –60 °C was obtained the desired butyrolactone with an enantiomeric excess of 82%. Yet, by increasing the temperature further to –70 °C, no additional effect occured.

3.3.5 Other ligands

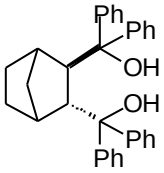
Studies were undertaken to assess the efficiency of ligands having other than the binaphthyl scaffold. To this end, the ligand precursors **129-135**[92] of different structural types were employed in the Al-mediated oxidation of 3-phenyl cyclobutanone (**32)** (Table 7). Compounds **129**[93] and **131** exhibited axial chirality, **131** also including central chirality. In addition, an ethane-1,2-diol derivative was used as well as ferrocenyl derivative **133**[94] and paracyclophanes **134**[95] and **135**[96] among which the latter three compounds displayed planar chirality.

[92] a)Enantiopure **132** was kindly provided by Prof. De Lucchi, University of Venice; b) for compound **130:** Ingo Schiffer, PhD thesis, RWTH, Aachen University, **2002**.
[93] Enantiopure **129** was kindly provided by Dr. Driessen-Hölscher, RWTH, Aachen University.
[94] Martin Kesselgruber, PhD thesis, RWTH, Aachen University, **2001**.
[95] Kirsten Wenz, PhD thesis, RWTH, Aachen University, **2002**.
[96] Thilo Focken, planned PhD thesis, RWTH, Aachen University.

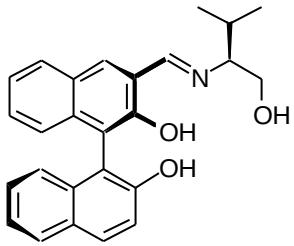
Table 6 Catalytic tests of the ligands **129-135**.[a]



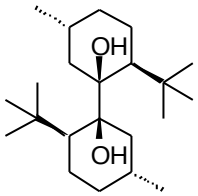
129



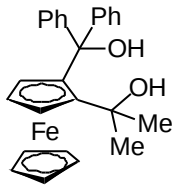
130



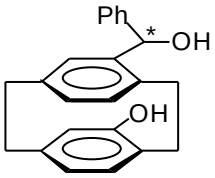
131



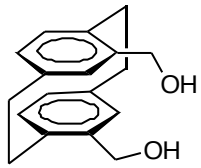
132



133



134



135

Entry	Ligand	Conv. [%]	*ee* [%]
1	(*S*)-**129**	100	70
2	(*R*,*R*)-**130**	100	*rac*
3	(R_{ax},*S*)-**131**	100	16
4	(1*S*,1'*S*)-**132**	63	7
5	(R_p)-**133**	8	*rac*
6	(R_p)-**134**	97	35
7	(S_p)-**135**	46	23

[a] Reaction conditions: according to general protocol GP5, Experimental section.

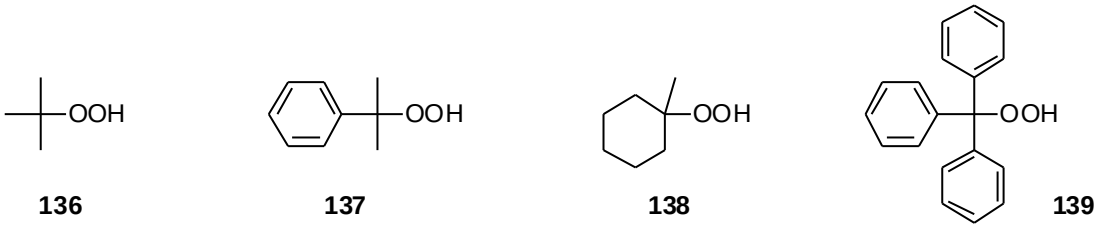
Diol **133** as ligand virtually prevented the oxidation to proceed (Entry 5,Table 6). Planar chirality is as well present in paracyclophanes **134** and **135**, which were capable to provide some enantioselectivity (Entry 6 and 7) even if ligand **135** brought about a conversion of 46% only. Concerning compound **131** as ligand, the result seems to suggest that a more than twofold coordinating ligand may decrease the enantiomeric excess (Entry 3). Among the compounds presented above only the atropisomeric biphenyl **129** gave results comparable with BINOL (Table 6, Entry 1). Accordingly, one could attribute the superior perfomance of **129** to its structural constitution similar to BINOL, i.e. two twisted aromatic planes. An important feature seems to be the free positions 3 and 3', respectively, vicinal to the hydroxy groups in **129**. Other biphenyl diols with substituents in positions 3 and 3' had previously been shown to provide lower enantioselectivity in the Al-mediated Baeyer-Villiger rearrangement.[69]

3.3.6 Influence of the hydroperoxide

The choice of the oxidant is of primary importance in asymmetric oxidation reactions. Hydroperoxides have frequently been employed but their use is mainly restricted to commercially available hydroperoxides such as *tert*-butylhydroperoxide or cumene hydroperoxide. Thus, *tert*-butylhydroperoxide has extensively been used in the Sharpless epoxidation of allylic alcohols[97] and in many other metal-mediated catalysis as well as in the production of propylene oxide by the oxirane process.[98] Even in industrial processes hydroperoxides found noticeble applications, as for instance, cumene hydroperoxide is an intermediate in the synthesis of phenol and acetone (Hock process).[99] However, little is known about the influence of the substitution pattern in oxidants, despite the fact that the synthesis of hydroperoxides is quite straightfoward. The corresponding alcohol is stirred for 3 days with a solution of 50% H_2O_2 with a small amount of H_2SO_4 followed by extraction in organic solvents.[100] Therefore, several catalytic tests using cyclohexyl hydroperoxide and trityl hydroperoxide were conducted with the Baeyer-Villiger oxidation of 3-phenyl cyclobutanone

[97] R. A. Johnson, K. B. Sharpless in *Catalytic Asymmetric Synthesis*, (Ed.: I. Ojima), VCH: Weinheim, **1993**, p. 103.
[98] R. A. Sheldon in *Applied Homogeneous Catalysis with Organometallic Compounds* (Eds.: B. Cornils, W. A. Hermanns), VCH: Weinheim 1996; vol. 1, p. 411.
[99] K. Weissermel, H. –J. Arpe, *Industrial Organic Chemistry*, VCH: Weinheim, **1998**, p 383.
[100] a) D. E. Bissing, C. A. Matuszac, W. E. McEwen, *J. Am. Chem. Soc.* **1964**, *86*, 3824; b) G. Lauterbach, W. Pritzkow, T. D. Tien, V. Voerckel, *J. Prakt. Chem.* **1988**, *330*, 933.

(**32**) and bicyclooctanone **24**, so as to get an insight into the importance of the steric hindrance of the oxidizing agents as regards the enantioselection.

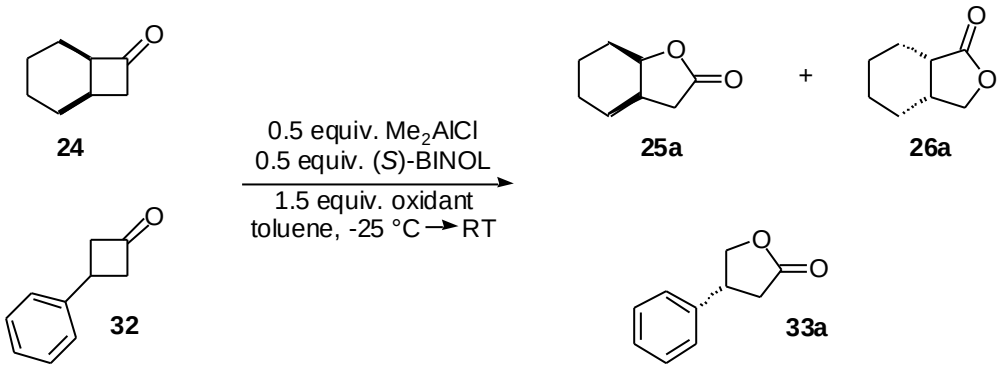


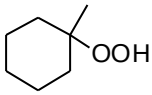
136 **137** **138** **139**

Scheme 37 Various hydroperoxide used in the Baeyer-Villiger reaction.

The experiments to examine the influence of the hydroperoxide were carried out in toluene in the presence of 0.5 equiv. of Me_2AlCl and 0.5 equiv. of enantiopure BINOL. The reaction mixture was stirred overnight and allowed to warm up from –25 °C to room temperature. Based on the results shown in Table 1, no general trend could be deduced, as long as an achiral hydroperoxide was employed. Although trityl hydroperoxide (**139**) (entry 8) was the best oxygen source in the case of **33**, the two regioisomeric products **25** and **26** were formed with the lowest enantioselectivity under these conditions. Furthermore, the lowest **25**:**26** ratio was not observed with the smallest hydroperoxide, TBHP, but with the sterically more demanding 1-methylcyclohexyl hydroperoxide **138**. In contrast, the bulkiest hydroperoxide, TrOOH, led to the highest **25**:**26** ratio.

Table 7 Influence of a various hydroperoxide in the Al-mediated Baeyer-Villiger oxidation.[a]

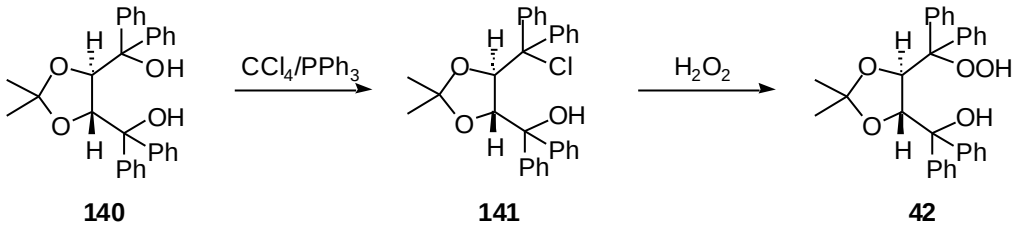


Entry	Substrate	Oxidant	*ee* of **25** [%]	*ee* of **26** [%]	Ratio **25**:**26**	*ee* of **33** [%]
1	**24**	TBHP	27 (1*R*,5*R*)	95 (1*S*,5*R*)	3.3	
2	**32**					64 (*S*)
3	**24**		36 (1*R*,5*R*)	94 (1*S*,5*R*)	2.1	
4	**32**					58 (*S*)
5	**24**	CHP	34 (1*R*,5*R*)	96 (1*S*,5*R*)	2.7	
6	**32**					71 (*S*)
7	**24**	TrOOH	22 (1*R*,5*R*)	80 (1*S*,5*R*)	4.5	
8	**32**					75 (*S*)

[a] Reaction conditions: according to general protocol GP5, Experimental Section.

Moreover, enantiomerically pure hydroperoxides have recently become versatile reactants in the synthesis of optically active compounds. The chiral hydroperoxides and peracids employed have been obtained by chromatographic resolution, by enzymatic kinetic resolution of racemic mixtures, or by derivatization of natural products, such as carbohydrates, with H_2O_2. Seebach reported on the synthesis of chiral TADDOL-hydroperoxide **42** obtained from

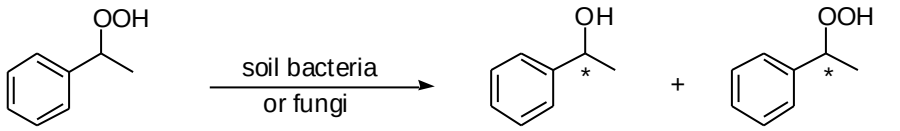
TADDOL **140** and H_2O_2 (Scheme 38).[101] Replacement of one OH group by an OOH group gave a stable, crystalline chiral hydroperoxide that was tested in three types of reactions: epoxidation of enones with base catalysis, sulfoxidation of methyl phenyl sulfide and Baeyer-Villiger reaction of bicyclic and tricyclic cyclobutanones.



140 **141** **42**

Scheme 38 Synthesis of a chiral TADDOL-hydroperoxide.

Adam et al. published a procedure based on enzymes to achieve enantiomerically pure hydroperoxide **142** (Scheme 39). By this means, optically active hydroperoxide was obtained with lipase, lipoxygenase or horseradish peroxydase. The problem of pure enzymes is that they are expensive and difficult to isolate, therefore research has focused on whole cell systems, that is bacteria, fungi, plant or animal cells, which are potentially available in large quantities through self-replication. With such a system, the kinetic resolution of a racemic hydroperoxyde had been successfully performed.[102]



rac - **142** (*R*) or (*S*)-**143** (*S*) or (*R*)-**142**

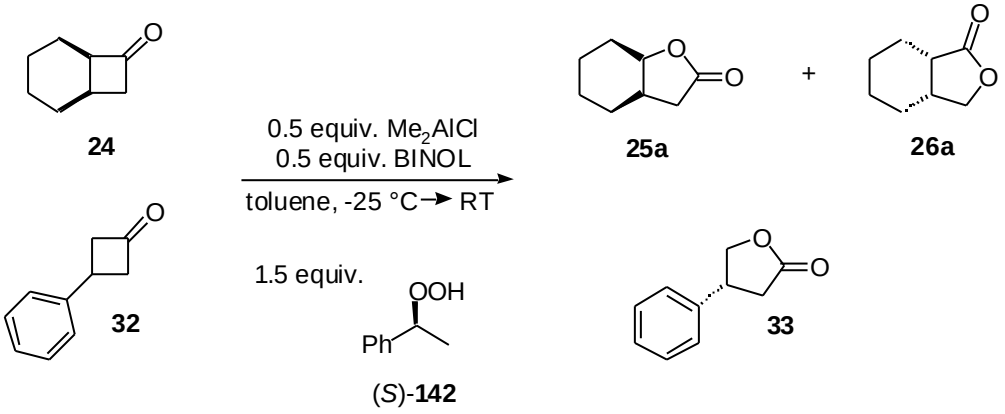
Scheme 39 Kinetic resolution of hydroperoxide.

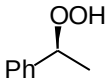
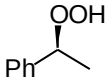
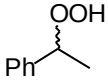
Consequently, the opportunity posed itself to examine how stereoselective the combination of a chiral hydroperoxide with each enantiomer of BINOL would be in the catalyzed asymmetric Baeyer-Villiger oxidation (Table 8). The incentive was to assess whether any cooperative effects would operate between the two chiral components, that is, the optically active hydroperoxide and the optically active ligand simultaneously coordinated to the metal

[101] a) M. Aoki, D. Seebach, *Helv. Chim. Acta* **2001**, *84*, 187; b) D. Seebach, A.K. Beck, A.Heckel, *Angew. Chem.* **2001**, *113*, 96; *Angew. Chem. Int. Ed.* **2001**, *40*, 92.
[102] W. Adam, B. Boss, D. Harmsen, Z. Lukacs, C. R. Saha-Möller, P. Schreier, *J. Org. Chem.* **1998**, *63*, 7598.

catalyst, and to identify which stereogenic centre would be responsible for the formation of the preferred enantiomer of the oxidation product. The chiral hydroperoxide (*S*)-(1-phenyl)ethyl hydroperoxide (**142**) was therefore tested.

Table 8 Use of (*S*)-(1-phenyl)ethyl hydroperoxide in the Al-mediated Baeyer-Villiger oxidation.[a]



Entry	Substrate	Oxydant	BINOL	*ee* of **25** [%]	*ee* of **26** [%]	Ratio **25**:**26**	*ee* of **33** [%]
1	**24**		(*S*)	5 (1*R*,5*R*)	89 (1*S*,5*R*)	11.2	
2	**32**						60 (*S*)
3	**24**		(*R*)	18 (1*S*,5*S*)	92 (1*R*,5*S*)	4.5	
4	**32**						51 (*R*)
5	**24**		(*S*)	11 (1*R*,5*R*)	89 (1*S*,5*R*)	8.3	
6	**32**						56 (*S*)

[a] Reaction conditions: according to general procedure GP5, Experimental Section.

Clearly, entries 2 and 4 in Table 8 revealed that the absolute configurations for the products (*S*)-**33** and (*R*)-**33** were determined by the chirality of the ligand. Furthermore, the value of the enantiomeric excess of the oxidation products differed in both experiments, which implicated cooperative effects between the chiral ligand and the chiral hydroperoxide as a

result of matched and mismatched combinations. This was also supported by the notable change in the **25**:**26** ratio from 11.2:1 to 4.5:1. Consequently, the enantiomeric excess achieved with the racemic (1-phenyl)ethyl hydroperoxide (entry 6) fell, after complete oxidation, between the *ee* values of the experiments with the pure enantiomers in entries 2 and 4.

3.3.7 Alternative oxidants

The replacement of the widely used oxidants hypochlorite and alkylhydroperoxide by hydrogen peroxide is being driven by environmentally and economical considerations, respectively.[103] The only byproduct when H_2O_2 is used is water but even if it is a strong oxidant, it reacts very slow and needs to be activated. One possible route involves the conversion to peroxyacids by reaction with a carboxylic acid or an anhydride.[104] Some attempts to generate peracids in situ have also been reported.[105] A method for the activation of H_2O_2 by using bicarbonate was described by Drago and co-workers: on the basis of NMR studies, they concluded that the active oxidant was peroxymonocarbonate formed by a labile preequilibrium reaction between bicarbonate and H_2O_2.[106] Another alternative may be the use of sodium carbonate peroxohydrate ($2Na_2CO_3 \cdot 3H_2O_2$). The principal use of commercially available sodium carbonate peroxohydrate is as a bleaching agent in domestic and laundry detergents. It dissolves rapidly in water and offers the advantage of a high concentration of active oxygen per unit volume of granulated product. The peroxohydrate does not need high solubility in order to react. It is just enough to have a suspension of it in THF or dichloromethane presaturated with water. The reaction can be accelerated by using ultrasonic radiation.[107]

A further anhydrous surrogate for hydrogen peroxide is bis(trimethylsilyl) peroxide (BTSP).[108] It is prepared from bis(trimethylsilyl) urea and urea/H_2O_2 adduct in dichloromethane. In comparison with other oxidants, BTSP has a low active oxygen content

[103] *Catalytic Oxidation with Hydrogen Peroxide* (Ed.: G. Strukul), Kluver Academic Publishers, Dordrecht, **1993**.
[104] a) *Organic Peroxide* (Ed.: W. Ando), Wiley: New York, **1992**; b) *Chemistry of Peroxide* (Ed.: S. Patai), Wiley: Chichester, **1983**.
[105] R. S. Drago, A. L. M. L. Mateus, D. Patton, *J. Org. Chem.* **1996**, *61*, 5693.
[106] For review on sodium percarbonate and sodium perborate: a) A. McKillop, W. R. Sanderson, *Tetrahedron* **1995**, *51*, 6145; b) J. Muzart, *Synthesis* **1995**, 1325; c) A. McKillop, W. R. Sanderson, *J. Chem. Soc., Perkin Trans 1*, **2000**, 471.
[107] X. Gao-Yang, *Acta Chim. Sin.* **1989**, *5*, 463.
[108] W. P. Weber, *Silicon Reagents in Organic Synthesis*, Springer-Verlag: New York, **1983**.

(BTSP, 9%; TBHP, 17.8%; H_2O_2, 47%); but it was demonstrated to be very effective in oxidative processes including those that employ a metal catalyst.[109] A particulary useful oxidation procedure was developed by Sharpless and Yudin, which used BTSP as a source of anhydrous H_2O_2 in the presence of rhenium oxide for epoxidation.[110]

Table 9 Screening of alternative oxidants.

Entry	Oxidant	Conversion %	*ee* %
1	PhIO	-	-
2	Li_2O_2	-	-
3	$NaCO_3$ $1/2H_2O_2$	-	-
4	$Na_2\{B_2(O_2)_2(OH)_4\}$	-	-
5	Urea H_2O_2	50	20
6[a]	Urea H_2O_2	100	8
7[b]	Urea H_2O_2	100	13
8	$(Me_3SiO)_2$	-	-

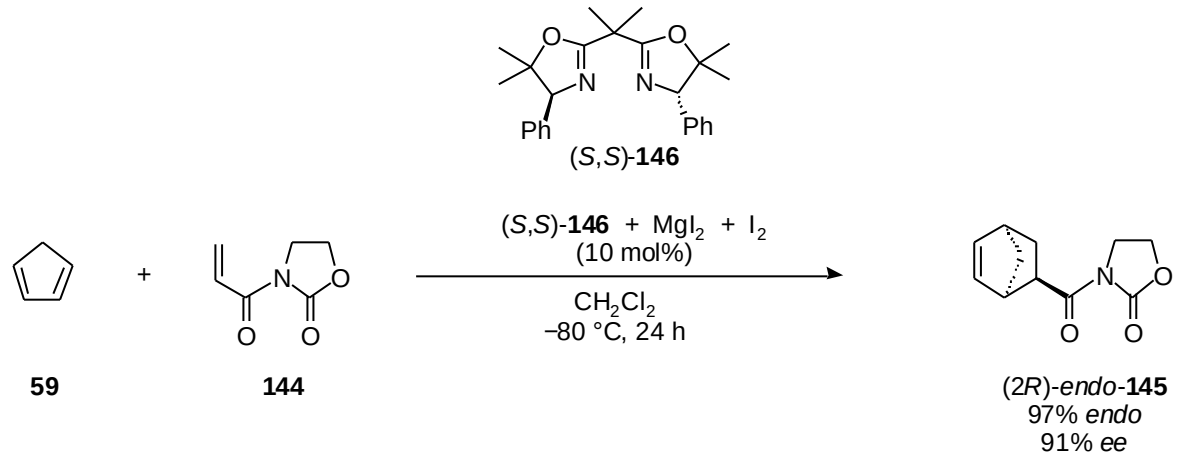
[a] 1 equivalent of [(*S*)-BINOL+Me_2AlCl] was used.
[b] 1 equivalent of [(*S*)-BINOL+Me_2AlCl] was used and MS 4Å were added.

In the Al-mediated Baeyer-Villiger oxidation, these alternative oxidizing agents were not effective as the results in Table 9 demonstrated. The urea H_2O_2 adduct proved to be the only oxidant that led to product, yet with lower activity and enantioselectivity than the usual hydroperoxide. Peroxygen did not seem to be compatible with the Al-system but in the form of monosubstituted peroxy specied ROOH.

[109] a) Y. Hayakawa, M. Uchiyama, R. Noyori, *Tetrahedron Lett.* **1986**, *42*, 877; b) F. Chemla, M. Julia, D. Uguen, *Bull. Soc Chim. Fr.* **1993**, *130*, 547; c) R. Irie, N. Hosoya, T. Katsuki, *Synlett* **1994**, 255; d) D. H. R. Barton, B. M. Chabot, *Tetrahedron* **1997**, *53*, 487.
[110] A. K. Yudin, K. B. Sharpless, *J. Am. Chem. Soc.* **1997**, *119*, 11536.

3.4 Asymmetric Baeyer-Villiger oxidation with chiral magnesium complexes

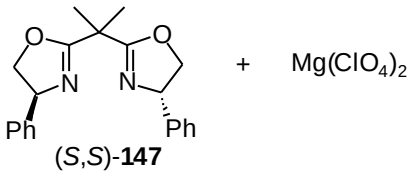
In recent years, many catalytic reactions have been established that involve a Lewis acid as the chiral mediator. Among these, also the main group metal magnesium has received attention for the use in 1,3-dipolar cycloadditions and Diels-Alder reactions. In 1992, Corey et al. reported the first example of a chiral magnesium catalyst: the cycloaddition of 3-acryloyloxazolidin-2-one (**144**) and cyclopentadiene (**59**) was performed in the presence of 10% of a chiral cationic bis(oxazoline) magnesium complex prepared in situ from bis(oxazoline) **146**, MgI_2 and I_2 as co-catalyst (Scheme 40).[111]



Scheme 40 First example of the use of a chiral Mg-complex.

The same catalytic system was applied in the synthesis of chiral cyanohydrins from aldehyde and trimethylsilyl cyanide.[112] Besides, further systematic investigation of the bis(oxazoline)-Mg combination were undertaken: Desimoni et al., for instance, reported on the enantioselective synthesis of either product enantiomer in the Diels-Alder addition of oxazolidinone **144** with cyclopentadiene (**59**) by using the (*S*,*S*)-**147**/$Mg(ClO_4)_2$ system depicted in Figure 8.[113]

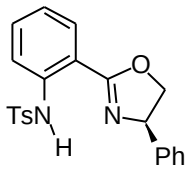
[111] E. J. Corey, K. Ishihara, *Tetrahedron Lett.* **1992**, *33*, 6807.
[112] E. J. Corey, Z. Wang, *Tetrahedron Lett.* **1993**, *34*, 4001.
[113] a) G. Desimoni, G. Faita, P. P. Righetti, *Tetrahedron Lett.* **1996**, *37*, 3027; b) G. Desimoni, G. Faita,A. G. Invernizzi, P. P. Righetti, *Tetrahedron* **1997**, *53*, 7671.



(*S*,*S*)-**147**

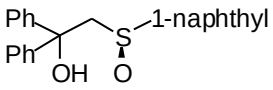
Figure 8 (*S*,*S*)-bis(oxazoline) **147**.

Usually, the (*S*)-*endo* product was obtained. However, simply by adding two equivalents of water to the complex, the system surprisingly furnished the opposite enantiomer, namely the (*R*)-*endo*-**145**. Other versions of the same reaction were reported by Fujisawaand co-workers, who used a (sulfonylamino)oxazoline **148** as ligand with a Grignard reagent (MeMgI) and I_2 as co-catalyst (Figure 9).[114] Llera applied a chiral Mg complex prepared from MgI_2 and chiral hydroxysulfoxides **149**.[115] Also this study was concentrated on the reaction of 3-acryloyl-1,3-oxazolidin-2-one as bidentate dienophile and cyclopentadiene as the prochiral diene.



+ MgI_2

148



+ MeMgI

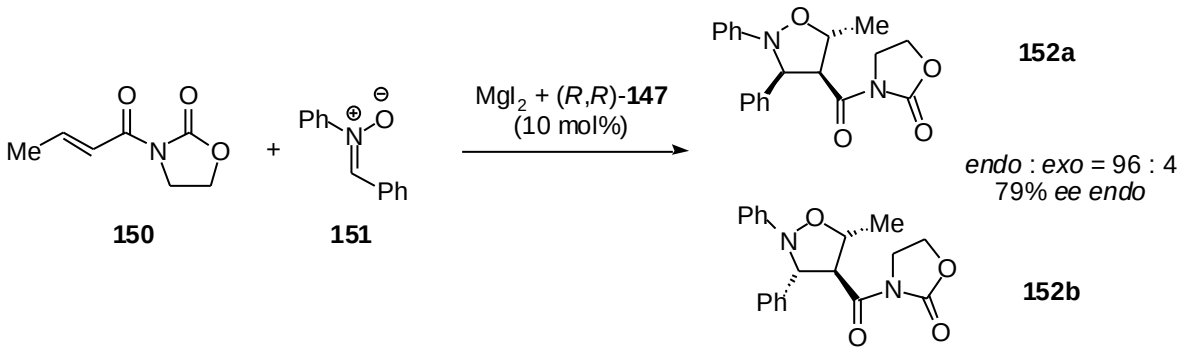
149

Figure 9 Chiral ligands used in combination with magnesium.

The application of bis(oxazoline)-magnesium complexes in the 1,3-dipolar cycloaddition was reported later on by Jørgensen and co-workers.[116] Nitrone **151** reacted with the oxazolidinone **150** in the presence of 10 mol% of a mixture of (*R*,*R*)-**147** and MgI_2 as shown below in Scheme 41. The presence of molecular sieves proved to be essential.[117] It acted not only as a

[114] a) T. Fujisawa, T. Ychiyanagi, M. Shimizu, *Tetrahedron Lett.* **1995**, *36*, 5031; b) T. Ychiyanagi, M. Shimizu, T. Fujisawa, *J. Org. Chem.* **1997**, *62*, 7937.
[115] M. Ordonez, V. Guerrero-de la Rosa, V. Labastida, J. M. Llera, *Tetrahedron: Asymmetry* **1996**, *7*, 2675.
[116] a) K. V. Gothelf, R. G. Hazell, K. A. Jørgensen, *J. Org. Chem.* **1996**, *61*, 346; b) K. V. Gothelf, R. G. Hazell, K. A. Jørgensen, *J. Org. Chem.* **1998**, *63*, 5483.
[117] As regards the role of MS in Lewis acid catalysis, see: a) M. Terada, Y. Matsumoto, Y. Nakamura, K. Mikami, *Chem. Soc., Chem. Commun.* **1997**, 281; b) G. H. Posner, H. Dai, D. S. Bull, J.-K. Lee, F. Eydoux, Y.

medium to remove water from the reaction mixture but it was also a reaction component itself which could influence the selectivity and reaction rate of a catalytic process. In accordance with this finding, the application of MS 4Å presaturated with water was a catalyst component, which induced the reversal of enantioselectivity.



Scheme 41 Mg-catalyzed 1,3 dipolar cycloaddition of nitrones with alkenes.

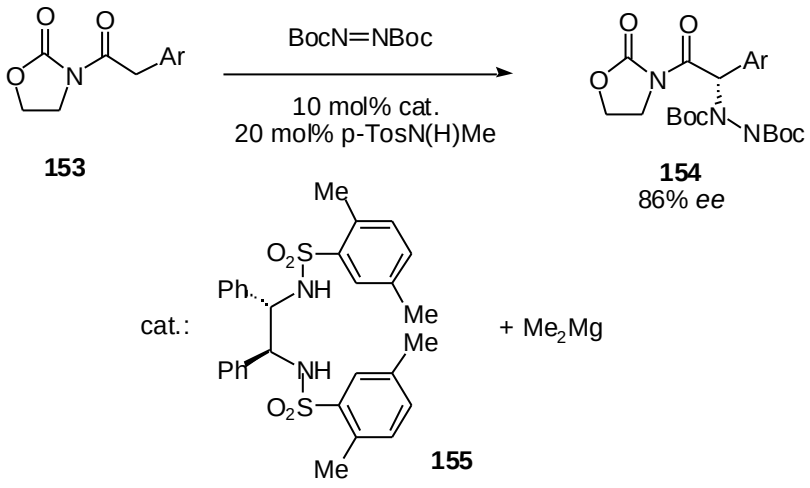
Besides in Diels-Alder type reactions,[118] magnesium was shown to be effective in other useful transformations. Sibi et al. reported the first examples of a highly enantioselective conjugate amine addition. *O*-Benzylhydroxyamine added to a pyrazole-derived crotonamide in the presence of a catalyst prepared from bis(oxazoline) and $MgBr_2 \cdot OEt_2$ with high enantiomeric excess (96%).[119] A species generated by treating (*S*,*S*)-bis(sulfonamide) **155** with dimethylmagnesium catalyzed the enantioselective enolate amination in simple carboxylate ester synthons as reported by Evans et al. (Scheme 42).[120]

Hishihara, W. Welsh, N. Pryor, S. Petr, *J. Org. Chem.* **1996**, *61*, 671; c) N. Iwasawa, Y. Hayashi, H. Sakurai, K. Narasaka, *Chem. Lett.* **1989**, 1581.

[118] For other examples of Mg-catalyzed Diels-Alder reactions, see: a) J. M. Takacs, E. C. Lawson, M. J. Reno, M. A. Youngman, D. A. Quincy, *Tetrahedron: Asymmetry* **1997**, *8*, 3037; b) Y. Honda, T. Date, H. Hiramatsu, M. Yamauchi, *Chem. Commun.* **1997**, 1411; c) S. Bromidge, P. C. Willson, A. Whiting, *Tetrahedron Lett.* **1998**, *39*, 8905.

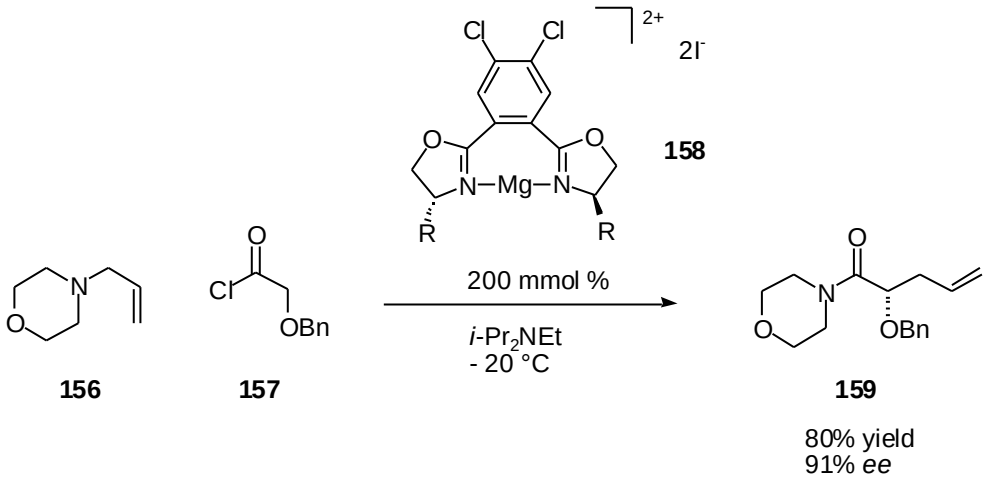
[119] M. P. Sibi, J. J. Shay, M. Liu, C. P. Jasperse, *J. Am. Chem. Soc*. **1998**, *120*, 6616.

[120] a) D. A. Evans, T. C. Britton, R. L. Dorow, J. F. Dellaria, *J. Am. Chem. Soc.* **1986**, *108*, 6395; b) D. A. Evans, T. C. Britton, R. L. Dorow, J. F. Dellaria, *Tetrahedron* **1988**, *44*, 5525; c) D. A. Evans, T. C. Britton,J. A. Ellman, R. L. Dorow, *J. Am. Chem. Soc.* **1990**, *112*, 4011; d) D. A. Evans, D. L. Rieger, M. T. Bilodeau, F. Urpi, *J. Am. Chem. Soc.* **1991**, *113*, 1047; e) D. A. Evans, S. G. Nelson, *J. Am. Chem. Soc.* **1997**, *119*, 6452.



Scheme 42 (*S*,*S*)-bis(sulfonamide)-magnesium complex in asymmetric conjugate amine addition.

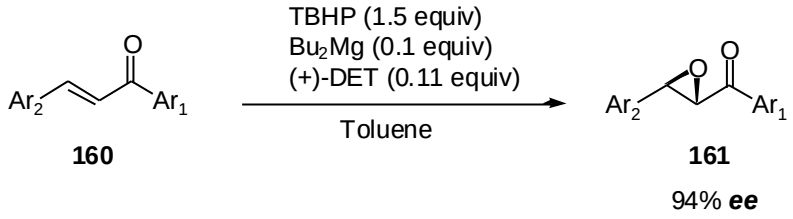
Very recently, Yoon and MacMillan published about the application of a complex derived from MgI_2 and a bis(oxazolinyl)aryl ligand in the asymmetric acyl-Claisen rearrangement.[121] In this case, the Lewis acid concept was demonstrated to play an important role in the design of an enantioselective variant of the [3,3]-sigmatropic bond reorganization. With MacMillan´s system very good enantioselectivity was obtained in the addition-rearrangement of benzyloxyacetyl chloride (**157**) with N-allylmorpholine (**156**) to give the Claisen product **159** (Scheme 43). However, 200 mol% of chiral complex were necessary and on reducing the catalyst loading to 50 mol% the *ee* dropped dramatically to 42%.



Scheme 43 Enantioselective acyl-Claisen rearrangement.

[121] T. P. Yoon, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2001**, *123*, 2911.

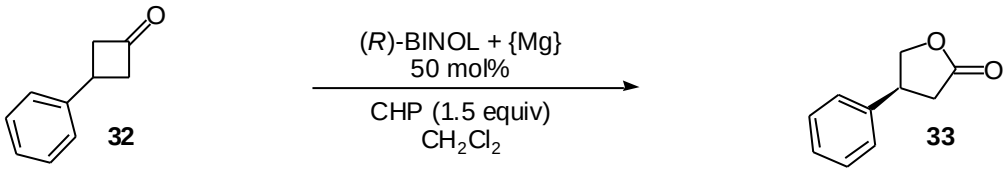
Only one Mg-catalyzed oxidation has been reported so far, namely the asymmetric epoxidation of chalcones by Jackson et al.[122] Different electron deficient alkenes were oxidized by using dibutylmagnesium together with diethyltartrate as chiral catalyst in combination with *t*-butylhydroperoxide (TBHP) as oxidant (Scheme 44).



Scheme 44 Asymmetric epoxidation of enones.

The active catalyst was believed to be a magnesium bis(alkoxide). Albeit leading to epoxides with up to 94% enantiomeric excess. This particular system was not especially effective for the epoxidation of aliphatic enones, achieving for such substrates only very poor conversions. The problem was overcome by modifying the ligand, i.e. by using bulkier ester derivatives.[123]

In the initial evaluation of Mg(II)-based complexes as chiral Lewis acid-mediators in the Baeyer-Villiger oxidation, the oxidation of 3-phenylcyclobutanone (**32**) by cumene hydroperoxide in the presence of a complex derived from Bu_2Mg and a chiral chelating ligand was chosen as model reaction (Scheme 45).[124]



Scheme 45 Magnesium-mediated Baeyer-Villiger reaction.

Both nitrogen containing ligands and diols were taken into account. A selection of the compounds employed is listed in Figure 10. Among them were bis(oxazoline)s, which have been employed successfully in many magnesium catalyzed transformations, sufonamides,

[122] C. L. Eston, R. F. W. Jackson, S. J. MacDonald, P. J. Murray, *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 410.
[123] O. Jacques, S. J. Richards, R. F. W. Jackson, *Chem. Commun.* **2001**,
[124] Reaction conditions: (*S*)-BINOL (0.1 mmol), solvent (5 mL), [Mg] (0.1 mmol), 3-phenylcyclobutanone **32** (0.2 mmol), CHP (0.3 mmol), −25°C to RT, 18 h.

which, by reaction of the amine proton with the butyl group of Mg, bound very tightly to the metal centre, and some diols such as hydrobenzoin, BINOL and its derivatives.

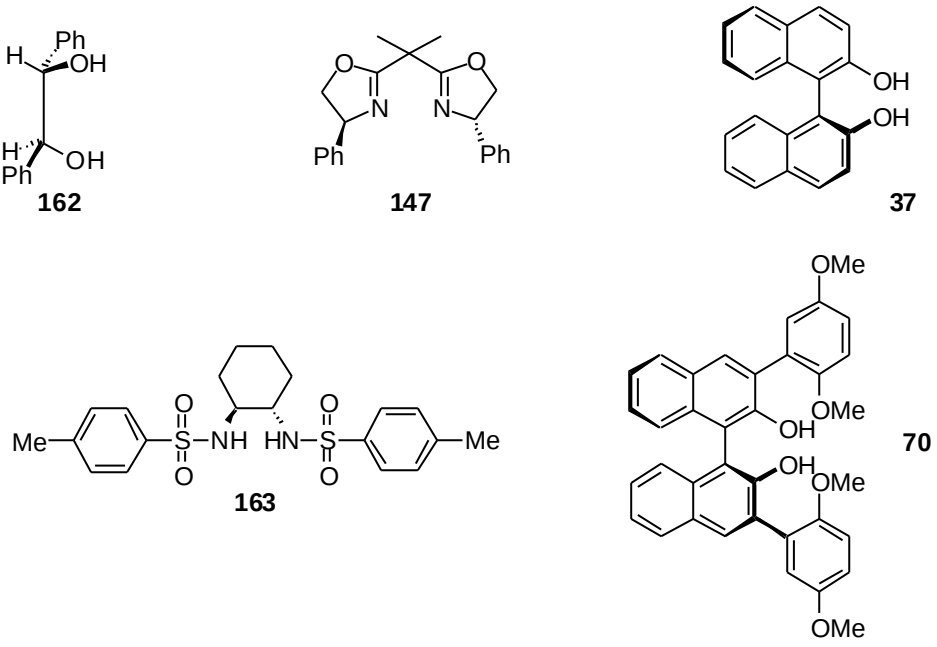


Figure 10 Compounds tested as ligands in Mg-mediated Baeyer-Villiger reaction.

Among all these compounds tested, only enantiopure BINOL proved useful in the enantioselective oxidation. With (*R*)-BINOL full conversion of **32** to the corresponding lactone **33** and 33% enantiomeric excess were achieved. In view of this result, it seemed appropriate to focus on a screening of different metal sources with BINOL as ligand. Thus, the applicability of various metal precursors in the oxygen transfer to prochiral substrates was examined. Interestingly, and in contrast to what was noticed in the case of the aluminium system, in which only one metal precursor, Me_2AlCl, was found to be suitable for the asymmetric Baeyer-Villiger oxidation, it was discovered that with many organomagnesium compounds notable enantiomeric excesses were obtained. Among various reagents surveyed, MeMgI and MgI_2 afforded the best results, i.e., full conversion and *ee* values up to 60 and 65%, respectively (entries 4 and 9 in Table 10). When, however, magnesium triflate was employed as precursor, the conversion to lactone was only 20% and no asymmetric induction was observed. Furthermore with the use of both anhydrous $MgCl_2$ and $MgSO_4$ the oxidation was completely inhibited. The superiority of MgI_2 may be attributed to the easier dissociation of an iodide anion from species such as L_2MgI_2 as already proposed by Corey at al. for his Mg

catalysis [125] It is in fact assumed that the iodide and triiodide ligands at magnesium are dissociated to give a highly activated twofold cationic intermediate. On the other hand, the counterion may be fundamental in determining the geometry of the active complex, as Desimoni stressed with respect to Mg-catalyzed dipolar cycloadditions.[126] For the Baeyer-Villiger reaction, the outcome of the oxidations with different metal sources shows that the nature of the Mg(II) compound strongly influences both activity and enantioselectivity as reported in Table 10. Moreover, it must be noted that high yields could be obtained.

Table 10 Asymmetric oxidation of 3-phenylcyclobutanone (**32**) mediated by various Mg precursors in combination with enantiopure BINOL.[a]

Entry	Magnesium source	Conv. (%) Yield [%]	*ee* (%)
1	Bu_2Mg	100	33
2	MeMgBr	100	49
3	PhMgBr	70	58
4	MeMgI	100 [93]	61
5	$Mg(OTf)_2$	20	*rac*
6	$MgSO_4$	10	*rac*
7	$MgCl_2$	7	*rac*
8	$MgBr_2$ OEt_2	80	50
9	MgI_2	100 [91]	65

[a] for reaction conditions see ref. 124.

A survey of different solvents revealed a clear dependency of the enantioselectivity on the type of solvent. The use of acetonitrile led to low conversion only. In 1,2-dichloroethane and chlorobenzene, the product had 60% and 55% *ee*, respectively. The solvent of choice, however, was dichloromethane, which allowed the formation of phenyl-γ-butyrolactone (**33**)

[125] E. J. Corey, Y. Matsumura, *Tetrahedron Lett.* **1991**, *32*, 6289; b) E. J. Corey, T.-P. Loth, T. D. Roper, M. D. Azimioara, M. C. Noe, *J. Am. Chem. Soc.* **1992**, *114*, 8292; c) E. J. Corey, W. Li, G. A. Reichard, *J. Am. Chem. Soc.* **1998**, *120*, 2330.
[126] G. Desimoni, G. Faita, A. Mortoni, P. Righetti, *Tetrahedron Lett.* **1999**, *40*, 2001.

with 65% *ee* (Table 11). By adding 10% of water, the reaction was completely inhibited while a coordinating media such as diethylether as cosolvent with CH_2Cl_2 (1:1 mixture), brought about lower conversion as well as a reduced enantioselection.

Table 11 Influence of the solvent in the asymmetric oxidation of 3-phenylcyclobutanone (**32**) mediated by MgI_2 in combination with enantiopure BINOL.[a]

Entry	Solvent	Conv. [%]	*ee* [%]
1	CH_2Cl_2	100	65
2	CH_2Cl_2 + H_2O (10:1)	no conv.	-
3	CH_2Cl_2 + Et_2O (1:1)	83	58
4	$ClCH_2CH_2Cl$	100	60
5	Toluene	100	35
6	Acetonitile	10	*rac*
7	Chlorobenzene	100	55
8	1,3,5-Trifluorotoluene	100	57

[a] for reaction conditions see ref.124.

The use of fluorinated compounds, such as trifluorotoluene (entry 8 in Table 11) did not prove to be more competitive than dichloromethane. The temperature influenced the extent of the enantioselectivity strongly. When the reaction was conducted at room temperature the enantioselection was very modest and 34% *ee* was achieved. However, by starting the reaction at –25 °C and then allowing the reaction mixture to warm to room temperature, the *ee* was increased to 65%, and no additional effect was observed at lower temperature.

Table 12 Temperature and enantiomeric excess.

Temperature [°C]	+25	0	–25	–78
ee [%]	34	51	65	65

Figure 11 reflects the evolution of conversion and enantioselectivity in the course of the enantioselective oxidation of 3-phenylcyclobutanone (**32**) with CHP in the presence of the catalyst derived from (*S*)-BINOL and MgI_2. The oxidation process was extremely fast at the beginning, the conversion being 75% after 1h. Then, the conversion slowly reached a plateau, whereas the *ee* value remained constant with time. This indicated that the species responsible for the enantioselection was always the same.

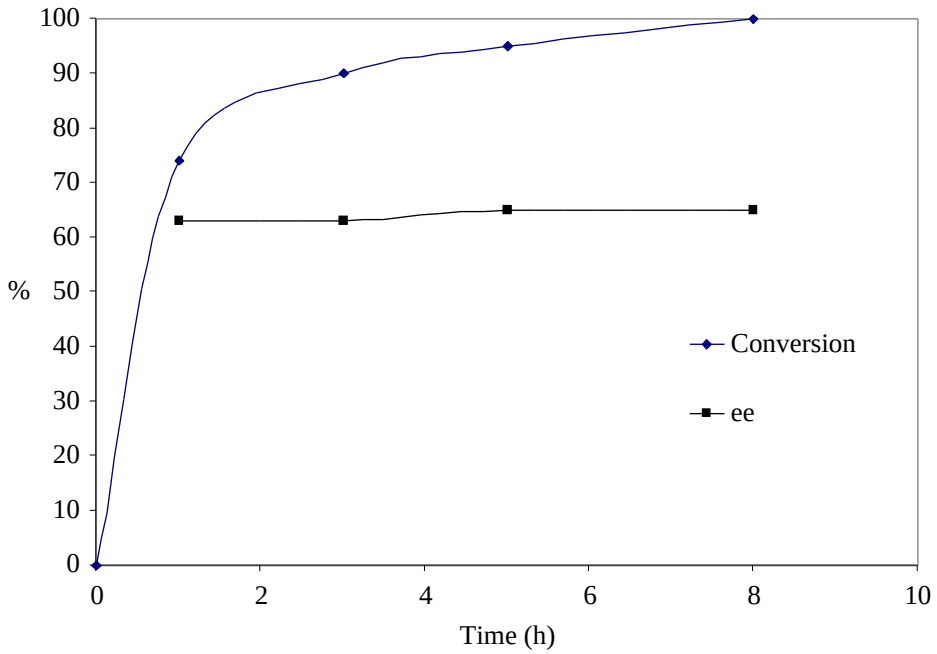
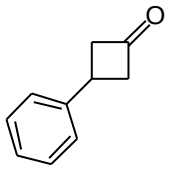
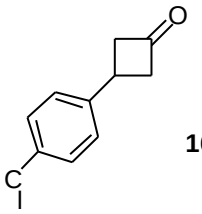
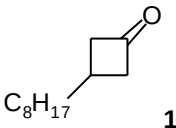
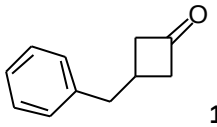
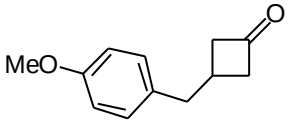
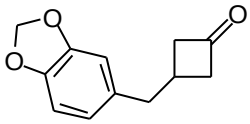


Figure 11 Evolution of conversion and enantioselectivity in the course of the reaction.

Table 13 shows the *ee* values of lactones that were obtained by complete oxidation of the corresponding prochiral cyclobutanones. With a substituent in position 3 of the cyclobutanones other than phenyl group, i.e. alkyl or benzyl groups, comparable results were achieved.

Table 13 Mg-mediated asymmetric oxidation of various prochiral cyclobutanones.[a]

Entry	Substrate	*ee* (%)	Configuration
1	 **32**	65	(–)-(*R*)
2	 **164**	63	(–)-(*R*)
3[a]	 **165**	52	(–)
4	 **166**	64	(–)-(*S*)
5	 **88**	61	(–)-(*S*)
6	 **90**	56	(–)-(*S*)

[a] The absolute configuration of the (-)-octyl-bearing lactone is supposed to be (*S*) since (*S*)-configured 3-pentyl and 3-hexylbutyrolactone exibited a negative rotation, too.[127]

In order to modify the Mg complex further, several additives were tested. The addition of 1 equivalent of I_2 had been shown to be benign for Diels-Alder reactions involving MgI_2 due to the dissociation of the iodide as a iodinate. Its addition in the Baeyer-Villiger oxidation, however, led a small decrease in the enantiomeric excess (62% instead of 65%). Also the addition of molecular sieves had a detrimental effect, contrary to the observation of Jørgensen

[127] H. Kosugi, K. Tagami, A. Takashi, H. Kanna, H. Uda, *J. Chem. Soc., Perkin Trans. 1* **1989**, 935.

and Desimoni, who found molecular sieves to be an essential part of their magnesium catalyst system. The presence of a base, such as DBU, or a silver salt, e.g. $AgSbF_6$, for exchanging the I^- counterion by SbF_6^- which proved advantageous in asymmetric Diels-Alder reactions effected an inhibition of the oxidation reaction. Only the presence of a stoichiometric amount of $AgNO_3$ allowed a slightly higher enantioselectivity (66% *ee*).

Attempts to increase the enantiomeric ratio by modifying the substitution pattern of the BINOL ligand failed. In fact, none of the substituted or modified binaphthols proved to be better than the non-substituted binaphthol. For instance, a BINOL derivative bearing bromo substituents in position 3 and 3' vicinal to the hydroxy groups inhibited the oxidation, while the same substituent in position 6 and 6' caused a drop in *ee* to 56%. The use of mono or diprotected BINOL (methoxy instead of hydroxy groups) as well as 2,2'-diaminobinaphthyl and BINAP afforded racemic products. At least 33% *ee* was achieved with Li di-BINOLate. As the use of only 0.5 eq. of Mg-BINOL was as effective as the stoichiometric variant of the oxidation (entries 2 and 3, Table 14), a further reduction of the catalyst loading was tried. Indeed, an experiment with phenyl cyclobutanone as substrate confirmed that complete conversion and an *ee* value of 63% was attainable by employing 25 mol% of the chiral mediator instead of 0.5 eq. (entry 1, Table 14).

Table 14 Influence of the catalyst loading in the asymmetric oxidation of cyclobutanone (**32**) mediated by MgI_2 in combination with enantiopure BINOL.

Entry	Catalyst loading [eq.] (Ratio Mg:BINOL)	*ee* [%]
1	0.25 (1:1)	62
2	0.5 (1:1)	65
3	1 (1:1)	60
4	0.5 (1:2)	67
5	1 (2:1)	58[a]

a. Conversion = 88%.

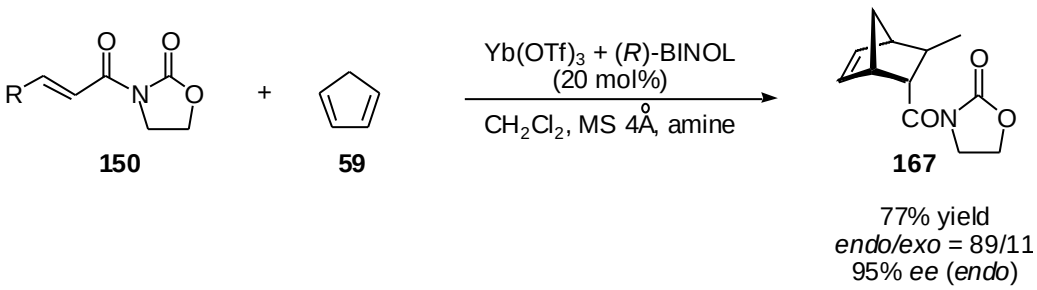
In order to get a deeper insight into the mechanism of the Mg-mediated Baeyer-Villiger reaction, we investigated the order of addition of substrate and oxidant, with the intention to

understand whether the intermediate was the BINOL-Mg complex with the ketone coordinated to the metal centre or alternatively a chirally modified metal peroxide. Interestingly, both experiments led to the same result. Thus, it must be assumed that the intermediary species that eventually afforded the product lactone, is in both cases the same.
Also the attempt to analyze the reaction by means of React-IR spectroscopy failed since all the species involved in this transformation possessed a carbonyl or -carboxyl group which made it impossible to distinguish all the different streching bands.

3.5 Baeyer-Villiger oxidation promoted by chiral ytterbium complexes

Lanthanides exhibit a strong affinity for heteroatoms such as nitrogen and oxygen and a large coordination number. These properties make them attractive Lewis acids for catalytic reactions. The special feature is that they will maintain their Lewis acidity even after being coordinated with a chiral ligand while metals such as Ti, Al, B, and Sn often loose this property as a result of coordinative saturation.

Kobayashi and co-workers studied Diels-Alder reactions using a catalyst prepared from $Yb(OTf)_3$, binaphthol (**37**) and a tertiary amine (Scheme 46).[128] It was discovered that the amine had a fundamental role and that bulky amines were required in order to achieve better enantioselection. The use of cis-1,2,6-trimethylpiperidine combined with molecular sieves led to the result reported in Scheme 46.[13]C NMR and IR spectroscopic studies suggested a structure in which the tertiary amine coordinated to phenolic protons of binaphthol.

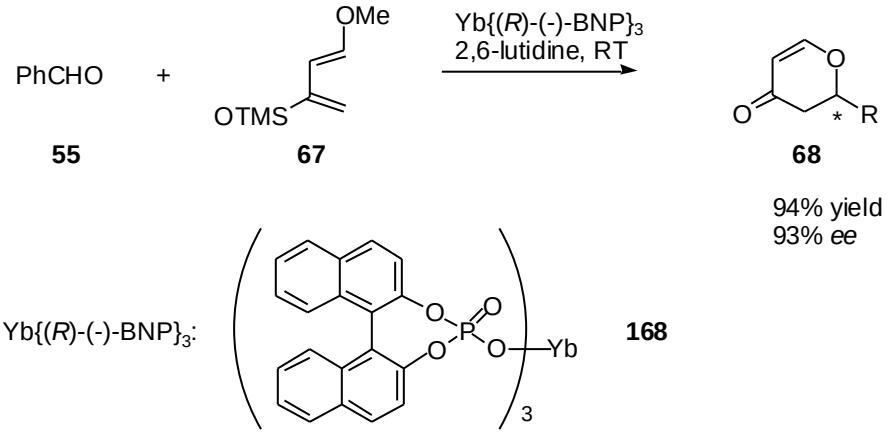


Scheme 46 BINOL-Yb complex as catalyst for Diels-Alder reaction.

[128] a) S. Kobayashi, I. Hachiya, H. Ishitani, M. Araki, *Tetrahedron Lett.* **1993**, *34*, 4535; b) S. Kobayashi, H. Ishitani, I. Hachiya, M. Araki, *Tetrahedron* **1994**, 50, 11623; c) S. Kobayashi, H. Ishitani, *J. Am. Chem. Soc.* **1994**, *116*, 4083.

With almost the same system it was also possible to carry out aza-Diels-Alder reactions.[129] In fact one of the peculiarities of the lanthanide catalysts was that catalytic processes were completed even in reactions using nitrogen-containing compounds, while most Lewis acids were decomposed or deactivated in the presence of basic nitrogen atoms. Thus, *N*-benzylidene-2-hydroxyaniline was reacted with pentadiene in the presence of the chiral Yb catalyst, prepared from $Yb(OTf)_3$, BINOL and DBU, combined with DTBP (2,6-di-*t*-butyl-4-methylpyridine) to give the corresponding tetrahydroquinoline derivative in 92% yield with high selectivity, namely a ratio *cis*/*trans* larger than 99/1 and 71% *ee*.

A chiral BINOL-derived ytterbium phosphate was developed by Inaga et al. and applied to asymmetric hetero Diels-Alder reactions of benzaldehyde (**55**) with Danishefsky´s diene **67** (Scheme 47).[130] In this case, the effect of the central metal ion of the chiral catalyst on the *ee* of the product, 2-phenyl-2,3-dihydro-4H-pyran-4-one (**68)**, was investigated. The result was that the degree of enantioselection was highly dependent on the ionic radius of a lanthanide ion. Since the reaction mixture was heterogeneous, addition of pyridine or pyridine derivatives was required in order to dissolve the catalyst and improve chemical yields and *ee*.

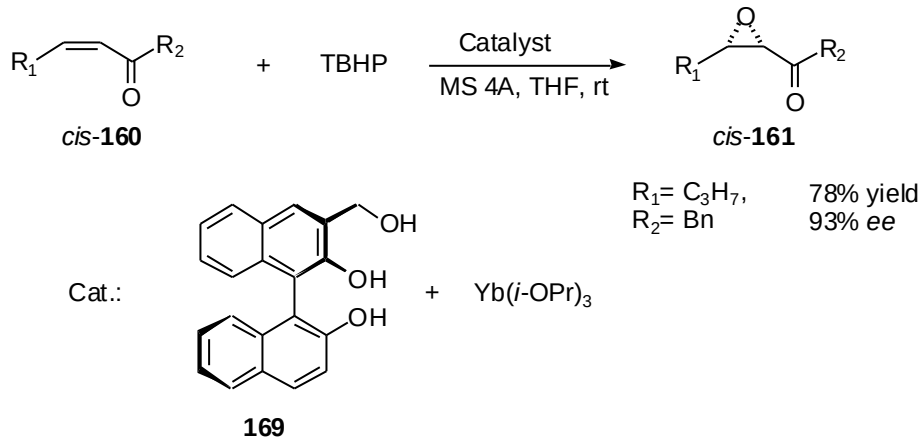


Scheme 47 BINOL derived ytterbium phosphate.

Jørgensen and co-workers developed an asymmetric variant of the 1,3-dipolar cycloaddition reaction using a Yb-PyBOX complex. Performing the reaction between alkenes and nitrones, enantiomeric excesses of up to 73% were obtained.[131] Shibasaki et al. reported the first

[129] H. Ishitani, S. Kobayashi, *Tetrahedron Lett.* **1996**, *37*, 7357.
[130] T. Hanamoto, H. Furuno, Y. Sugimoto, J. Inanaga, *Synlett* **1997**, 79.
[131] A. I. Sanchez-Blanco, K. V. Gothelf, K. A. Jørgensen, *Tetrahedron Lett.* **1997**, *38*, 7923.

efficient synthesis of *cis*-epoxyketone **161** from *cis*-enone **160** by use of the catalyst derived from Yb-triisopropanolate and (*R*)-3-(hydroxymethyl)-1,1'-bi-2-naphthol **169** (Scheme 48).[132]



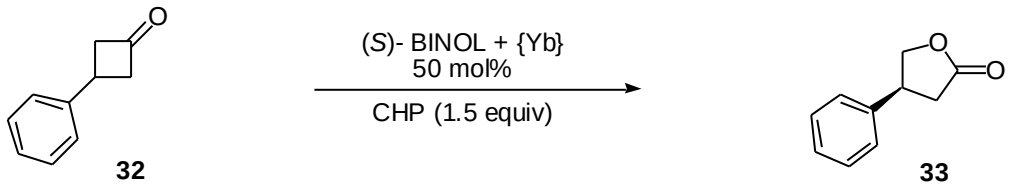
Scheme 48 Synthesis of *cis*-epoxyketone *cis*-**161**.

In view of these examples for asymmetric Yb-catalyses with carbonyl substrate, a chiral system based on ytterbium was envisioned as useful for the asymmetric Baeyer-Villiger oxidation of prochiral cyclobutanones using hydroperoxides such as cumene hydroperoxide. The reaction of 3-phenylcyclobutanone with CHP in the presence of a catalyst generated in situ from (*R*)-BINOL and Yb(*i*-OPr)$_3$ in toluene provided the expected product of oxygen insertion with full conversion and 33% *ee*. Substitution of the metal precursor with $YbCl_3$ and $Yb(OTf)_3$, however, decreased or prevented conversion in the oxidation reaction.

In Table 15, the screening of different solvents is reported. With toluene as well as dichloromethane and diethylether, full conversion to the corresponding lactone was observed but with a different degree of enantioselection, toluene being the best solvent. The use of coordinating solvents such as ether did not suppress the activity. In contrast, the addition of water (entry 4) or the use of acetonitrile (entry 6) both virtually reduced the enantiomeric discrimination and decreased the activity.

[132] S. Watanabe, T. Arai, H. Sasai, M. Bougauchi, M. Shibasaki, *J. Org. Chem.* **1998**, *63*, 8090.

Table 15 Influence of the metal precursor and the solvent on the *ee* of **33**.[a]



Entry	Metal precursor	Solvent	Conversion [%]	*ee* [%]
1	$YbCl_3$	toluene	30	*rac*
2	$Yb(OTf)_3$	toluene	no conv.	-
3	Yb(*i*-OPr)$_3$	toluene	100	33
4	Yb(*i*-OPr)$_3$	toluene + H_2O (9:1)	32	4
5	Yb(*i*-OPr)$_3$	CH_2Cl_2	100	23
6	Yb(*i*-OPr)$_3$	CH_3CN	66	14
7	Yb(*i*-OPr)$_3$	Et_2O	100	28

[a] Reaction conditions: (*S*)-BINOL (0.1 mmol), solvent (5 mL), [Yb] (0.1 mmol), 3-phenylcyclobutanone **32** (0.2 mmol), CHP (0.3 mmol), −25°C to RT, 18 h.

Kobayashi and Inanaga stressed the importance of an additive as regards to activity and stereoselectivity for lanthanide catalysts. Therefore it was investigated whether the use of a base could show the same effect in the Baeyer-Villiger oxidation. Unfortunately, the addition of an amine led to a completely inactive species. Other additives, different from a base, such as molecular sieves or a silver salt were also tried, but while the first one seemed to have no influence at all, the second entirely stopped the reaction (Table 16).

Table 16 Effect of the additives.[a]

Additive	Conversion (%)	*ee* (%)
NEt_3 (0.5 eq.)	100	*rac*
(+)$PhEtNH_2$	72	6
(-)$PhEtNH_2$	79	8
MS 4Å (50 mg)	100	28
$AgSbF_6$	5	*rac*

[a] Reaction conditions: (*S*)-BINOL **37** (0.1 mmol), solvent (5 mL), [Yb] (0.1 mmol), additive, 3-phenylcyclobutanone (**32**) (0.2 mmol), CHP (0.3 mmol), −25°C to RT, 18 h.

The test oxidation was carried out also with other sources of chirality as for instance diethyltartrate, hydrobenzoin, bimenthol, protected BINOL, a sulfonamide and amino acids. However, BINOL appeared again to be the ligand of choice.

It is believed that bidentate coordination is necessary to obtain high selectivities in many chiral lanthanide-catalyzed reactions. In the attempted Baeyer-Villiger oxidation, even with monodentate coordination, at least some level of enantioselection has been achieved. These interesting screening results could be taken as starting point for further investigation in the future.

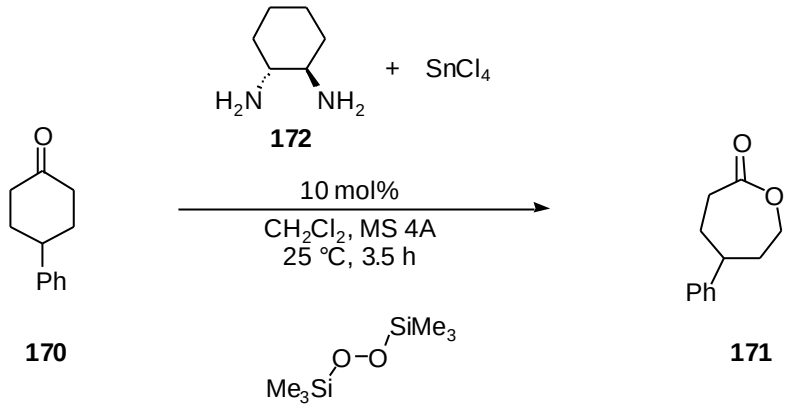
3.6 Tin-catalyzed asymmetric Baeyer-Villiger oxidation

$SnCl_4$ is classified as a strong Lewis acid and is used extensively in organic synthesis as Lewis acid for enhancing a variety of reactions. It interacts preferentially with hard oxygen and nitrogen bases, and it is preferred over boron, aluminium and titanium Lewis acids because it is monomeric, highly soluble in organic solvents and relatively easy to handle.

A tin based catalytic version of the Baeyer-Villiger oxidation of substituted cyclohexanones employing trimethylsilylperoxide as oxidant was developed by Shibasaki and co-workers.[133] Up to 82% of yield of lactones were achieved using a diamine as ligand and $SnCl_4$ as metal

[133] R. Göttlich, K. Yamakoshi, H. Sasai, M. Shibasaki, *Synlett* **1997**, 971.

precursor. Of the various amines used *trans*-1,2-(diamino)cyclohexane (**171**) gave the best result (Scheme 49). A major side product of this reaction is a ketone peroxide, whose formation may be minimized by addition of molecular sieves.



Scheme 49 Tin catalyzed Baeyer-Villiger oxidation.

Another variant which makes use of a heterogeneous catalyst base on a Sn-zeolite was recently reported by Corma et al.[27,134] Selective oxidation of cyclic ketones with hydrogen peroxide was made possible upon incorporation of 1.6% (weight) of tin into the framework of a zeolite beta. After an IR analysis of different metals, tin was selected, because, being a Lewis acid, it activated the ketone carbonyl group. Other metals, including transition metals, tended to activate hydrogen peroxide rather than the substrate, thereby leading to unwanted by-products.

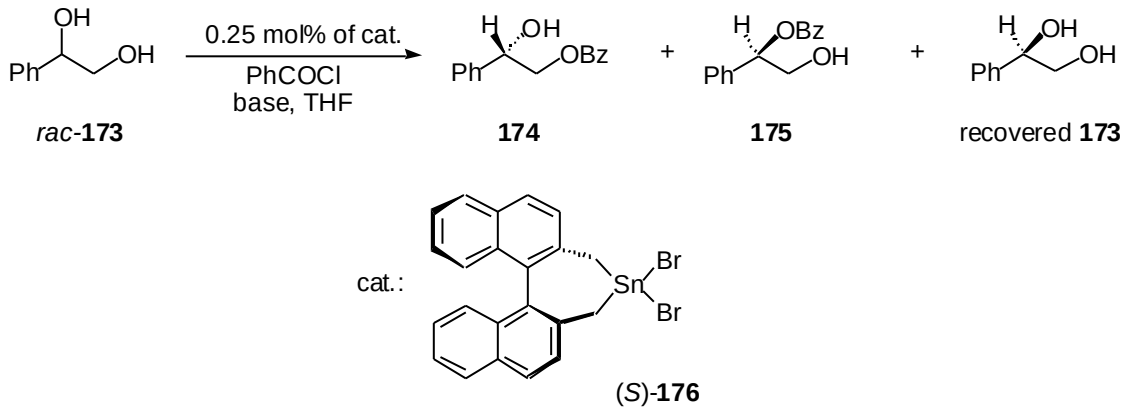
On the basis of these stimulating examples on tin catalyzed Baeyer-Villiger reactions and the numerous asymmetric tin catalyzed reactions,[135] the design of an efficent asymmetric catalyst for the enantioselective version of the Baeyer-Villiger oxidation was envisaged. The starting point was the oxidation of a test substrate, 3-phenylcyclobutanone (**32**), using as catalyst the simple in situ combination of a chiral ligand, for instance a diol or a nitrogen-containing ligand and the appropriate tin precursor. As was already mentioned in the case of the Al-

[134] A. Corma, M. T. Navarro, L. Nemeth, M. Renz, *Chem. Commun.* **2001**, 2190.

[135] For enantioselective transformation with $Sn(OTf)_2$, see: a) T. Mukayama, N. Minowa, *Bull. Chem. Soc. Jpn.* **1987**, *60*, 3697; b) S. Kobayashi, Y. Tsuchiya, T. Mukayama, *Chem. Lett.* **1991**, 541; c) S. Kobayashi, M. Horibe, Y. Saito, *Tetrahedron* **1994**, *50*, 9629; d) for enantioselective protonation with $SnCl_4$ and enantiopure BINOL, see: c) K. Ishihara, M. Kaneeda, H. Yamamoto, *J. Am. Chem. Soc.* **1994**, *116*, 11179; d) K. Ishihara, S. Nakamura, M. Kaneeda, H. Yamamoto, *J. Am. Chem. Soc.* **1996**, *118*, 12854; for isomerization, see: e) K. Ishihara, H. Nakamura, S. Nakamura, H. Yamamoto, *J. Org. Chem.* **1998**, *63*, 6444; for SEM addition reaction, see: f) K. Ishihara, H. Nakamura, H. Yamamoto, *J. Am. Chem. Soc.* **1999,** *121*, 7720.

mediated Baeyer-Villiger oxidation, the choice of the suitable metal precursor was fundamental. Some experiments have already been carried out with tin tetrachloride.[69] The question was if a metal precursor bearing a less coordinating anion, such as tin triflate, or a one with a stucture similar to the aluminium one, such as dimethyltin dichloride, would be appropriate. Different ratios of BINOL ligand to metal have been tested in the standard oxidation of ketone **32** in toluene, but in all cases only little conversion to the corresponding lactone was observed with no enantioselectivity. Hence, this attampt was not further persued.

On the other hand, an interesting organotin compound was developed for the kinetic resolution of 1,2-diols. The (*S*)-4,4-dibromo-4,5-dihydro-3H-dinaphto[2,1-c:1',2'-e]stannepin (**176**)[136] was employed in the resolution of racemic 1-phenyl-1,2-ethanediol (**173**) with benzoyl chloride as depicted in Scheme 50. A remarkable effect on the *ee* of the product was observed when an inorganic base was chosen − the best one being sodium carbonate − and a small portion of water was used.

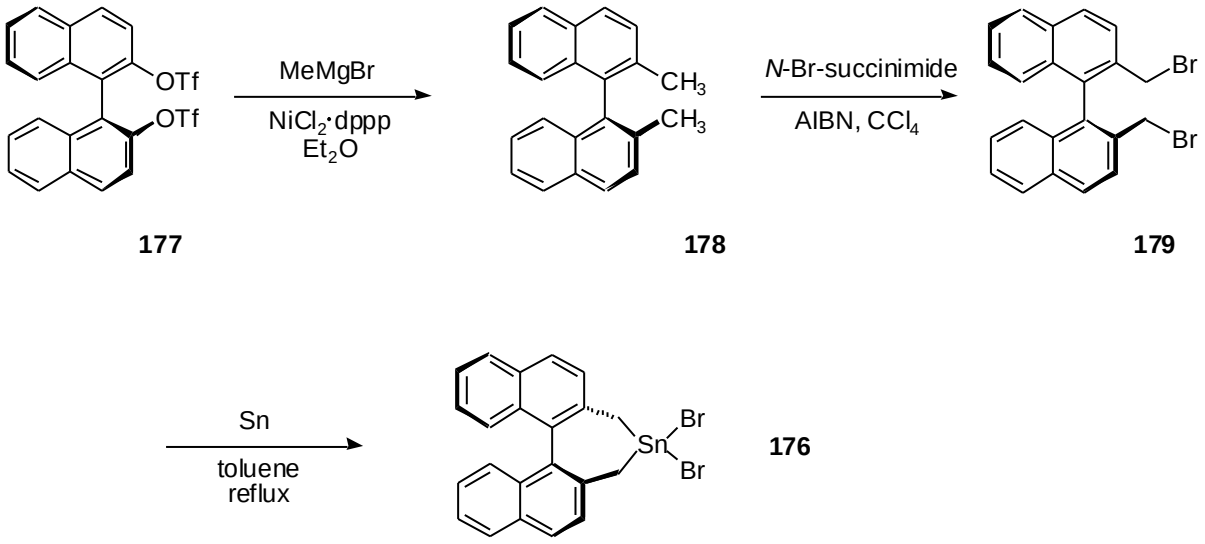


Scheme 50 Kinetic resolution of *rac*-**173**.

This compound was then often used as an intermediate in the synthesis of chiral tin hydride reagents which were employed in the radical reduction of organic halides[139,137] or as a precursor of dilithiobinaphthyl, which by subsequent reaction with electrophiles provided substituted binaphthyls.[138] Binaphthyl derivative **176** was synthesized according to the procedure reported by Nanni and Curran as shown in Scheme 51.[139] Starting from enantiopure

[136] a) R. Noyori, M. Kitamura, K. Takemoto, *Japan Kokai Tokkyo Koho JP* 04-91093, **1992**; *Chem. Abst.* **1992**, *117*, 171695u; b) U.-M. Gross, M. Bartels, D. Kaufmann, *J. Organomet. Chem.* **1988**, *344*, 277.
[137] M. Blumenstein, K. Schwarzkopf, J. O. Metzger, *Angew. Chem.* **1997**, *109*, 245; *Angew. Chem. Int. Ed.* **1997**, *36*, 235.
[138] J. M. Chong, G. K. MacDonald, S. B. Park, S. H. Wilkinson, *J. Org. Chem.* **1993**, *58*, 1266.
[139] a) D. Nanni, D. P. Curran, *Tetrahedron: Asymmetry* **1996**, *7*, 2417; b) N. Maigrot, J.-P. Mazaleyrat, *Synthesis* **1985**, 317.

BINOL-triflate **177**, reaction with methylmagnesium bromide provided the corresponding 2,2'-dimethyl-1,1'-binaphthyl (**178**) which was finally subjected to Ziegler-Wohl bromination. The 2,2'-bromomethyl-1,1'-binaphthyl (**179**), thus obtained, reacted with tin powder in refluxing toluene in the presence of trace amount of water to give the desired dibromostannepin (**176**).



Scheme 51 Synthesis of (*S*)-4,4-dibromo-4,5-dihydro-3H-dinaphto[2,1-c:1',2'-e]stannepin.

Binaphthyl derivative **176** was then used as a chiral Lewis acid in the Baeyer-Villiger oxidation of the prochiral 3-phenylcyclobutanone (**33**). The reaction was carried out under nitrogen in dry dichloromethane with cumene hydroperoxide (**137**) as oxidant, employing 0.5 equivalent of **176**. However, only traces of product were detected by gas chromatographic analysis and almost likely, the Lewis acidity of this metal complex was not suitable for the oxidation of ketones. Even exchanging the bromine substituents with a less coordinating anions such as triflate or hexafluoroantimoniate did not show any positive effect.

3.7 Attempts towards an asymmetric Baeyer-Villiger with H_2O_2

3.7.1 Transition metal-based Lewis acid catalysts

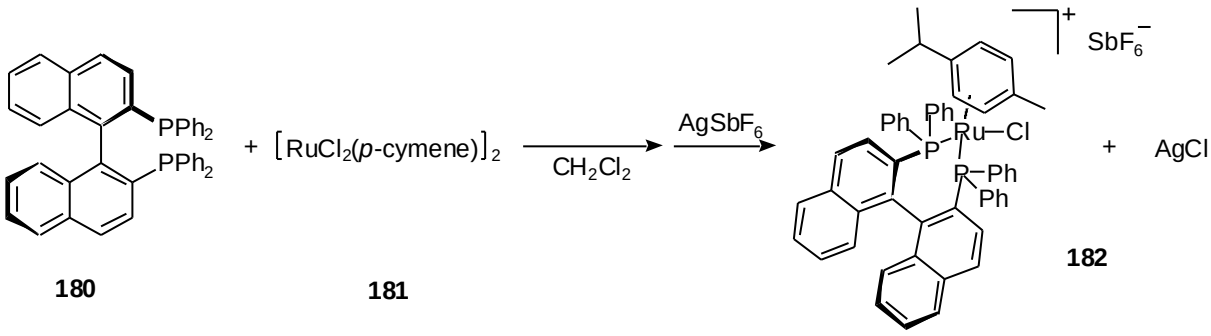
The use of main group metals in asymmetric catalysis has the advantage that these starting materials are generally cheap, easy to handle and, in some cases, stable to air. Furthermore, the active complex may be generated in situ. On the other hand, they are often sensitive to water and sometimes tend to ligate to each other, to scramble the ligands and to form oligomeric species. Moreover, the achiral Lewis acid precursor is also catalytically more active and hence can compete with the chiral species for the formation of the products. As a consequence, much effort is focussed on the search of stable catalysts with well-defined structures.

Lewis acid (LA) activation of a substrate is generally thought to be proportional to the electron-withdrawing properties of the LA. For instance, the presence of a positive charge on the metal centre is expected to enhance the required electronic displacement and to provide the necessary Lewis acidity. Tuning the Lewis acidity of the transition metal may be a fairly rational process, in view of the fact that different reactions require various degrees of Lewis acidity. For example, a strong activation is necessary for the classical Diels-Alder reaction, whereas milder Lewis acids are required in Mukaiyama reactions and Danishefsky-type hetero-Diels-Alder reactions.

Since the first report of transition metal-catalyzed stereoselective Diels-Alder reactions,[140] there has been a continuous developement of new ligands and new complexes that may be used for this reaction and, among these, some ruthenium complexes have proved to be very promising.[141] Moreover, organometallic ruthenium compounds are becoming increasingly important as catalysts in many other organic reactions.[142] Ruthenium(II) complexes are usually robust, air-stable, water-insensitive, diamagnetic (d^6) octahedral compounds. All of these properties make them very attractive for modification and application as a Lewis acid,

[140] D. Carmona, M. P. Lamata, L. A. Oro, *Coord. Chem. Rev.* **2000**, *200*, 717.
[141] a) E. P. Kundig, C. M. Saudan, G. Bernardinelli, *Angew. Chem.* **1999**, *111*, 1298; *Angew. Chem. Int. Ed.* **1999**, *38*, 1220; b) D. L. Davies, S. A. Fawcett, S. A. Garrat, D. R. Russel, *Chem. Commun.* **1997**, 1315.
[142] a) H. Brunner, *Angew. Chem.* **1999**, *111*, 1248; *Angew. Chem. Int. Ed.* **1999**, *38*, 1195; b) R. Noyori, S. Hashiguki *Acc. Chem. Res.* **1997**, *30*, 97; c) J. W. Faller, M. R. Mazzieri, J. T. Nguyen, *Pure Appl. Chem.* **1994**, *66*, 1463; d) H. Brunner, *Adv. Organomet. Chem.* **1980**, *18*, 151.

and several approaches have been reported in the literature. Chiral arene ruthenium complexes are potentially capable of catalytic asymmetric synthesis. One approach to the synthesis of such chiral compounds consitsts of binding a chiral bidentate auxiliary ligand to an arene-RuCl fragment, so as to generate a stereogenic metal centre.[143] Faller et al. have explored the chemistry of cationic chiral at-metal complexes and their application in Diels-Alder reactions.[144] Half sandwich complexes of ruthenium, osmium and iron, comprising BINAP or the corresponding monooxide or QUINAP, have also been reported by Faller et al.[145] The complex is generated by reaction of enantiopure BINAP (**180**) with cymene rutheniumdichloride dimer $[RuCl_2(p\text{-cymene})]_2$ (**181**) in dichloromethane. Subsequent treatment with silver antimonate leads to the abstraction of one chloride ligand and the formation of the active complex **182** (Scheme 52). The obtained 16-electron Lewis acid is a very efficient catalyst in the Diels-Alder reaction. In the case of a heterobidentate ligand, the chelation leads to the formation of a stereogenic centre at the metal and thus opens up the access to diastereomeric products.



Scheme 52 Preparation of the chiral cationic complex [RuCl((*R*)-BINAP)(*p*-cymene)]*S*bF[6].

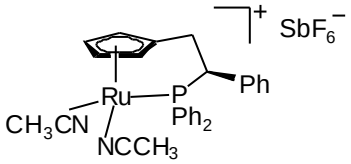
Ruthenium has also been used in catalytic oxidations in combination with salen, porphyrins or other nitrogen containing ligands,[146] often applying $NaIO_4$as oxidant,[147] but it was also found to activate hydrogen peroxide.[148] The discovery of efficient and practical methods for oxidations that utilize aqueous H_2O_2 as terminal oxidant remains an important objective in

[143] K. Mashima, K. Kusano, N. Sato, Y. Matsumura, K. Nozaki, H. Kumobayashi, N. Sayo, Y. Hori, T. Ishizaki, S. Akutagawa, H. Takaya, *J. Org. Chem.* **1994**, *59*, 3064.
[144] a) J. W. Faller, B. J. Grimmond, *Organometallics* **2001**, *20*, 2454; b) J. W. Faller, B. J. Grimmond, D. G. D´Alliessi, *J. Am. Chem. Soc.* **2001**, *123*, 2525.
[145] a) J. W. Faller, J. Parr, *Organometallics* **2001**, *20*, 697; b) J. W. Faller, B. P. Patel, M. A. Albrizio, M. Curtis, *Organometallics* **1999**, *18*, 697.
[146] For a review on ruthenium catalyzed oxidations, see: T. Naota, H. Takaya, S.-I. Murahashi, *Chem. Rev.* **1998**, *98*, 2599.
[147] a) C. Augier, L. Malara, V. Lazzeri, B. Waegel, *Tetrahedron Lett.* **1995**, *36*, 8775; b) N. End, A. Pfalz, *Chem. Commun.* **1998**, 589; c) N. End, L. Macko, M. Zehnder, A. Pfalz, *Chem. Eur. J.* **1998**, *4*, 818.
[148] R. M. Stoop, S. Bachmann, M. Valentini, A. Mezzetti, *Organometallics* **2000**, *19*, 4117.

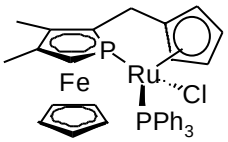
synthetic chemistry.[149] Several catalysts have been identified for peroxide based oxidations, in particular epoxidations.[150]

An analogous to complex **182** depicted in Scheme 52 was synthesized using (*S*)-tolyl-BINAP as phosphine ligand and $[RuCl_2(p\text{-cymene})]_2$ (**181**). With this complex and with ruthenium complexes **183**[151] and **184**[152] shown in Table 17, the catalytic activity in the Baeyer-Villiger oxidation of 3-phenylcyclobutanone (**32**) was tested. However, none of these complexes was able to promote the conversion to the respective lactone.

Table 17 Ruthenium complexes tested in the Baeyer-Villiger oxidation.



183



184

Entry[a]	Catalyst	Additive	Oxidant
1	**182**	-	H_2O_2 (30%)
2	**183**	-	H_2O_2 (30%)
3	**184**	-	CHP
4	**184**	-	H_2O_2 (30%)
5	**184**	$AgSbF_6$	CHP
6	**184**	$AgSbF_6$	H_2O_2 (30%)

[a] Reaction conditions: cat. (0.01 mmol), dichloromethane (5 mL), 3-phenylcyclobutanone (**32**) (0.2 mmol), oxidant (0.3 mmol).

[149] G. Strukul in *Catalytic oxidations with hydrogen peroxyde as oxidant*, (Ed. G. Strukul), Kluwer, Dordrecht, **1992**.

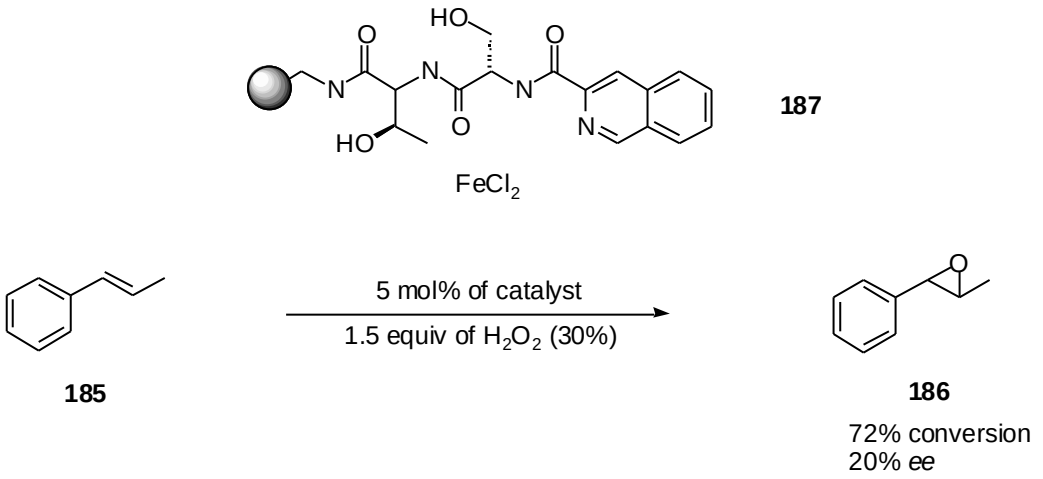
[150] Methyltrioxorhenium catalysts: a) J. Rudolph, K. L. Reddy, J. P. Chiang, K. B. Sharpless, *J. Am. Chem. Soc.* **1997**, *119*, 6189; b) W. A. Herrmann, R. W. Fischer, D. W. Marz, *Angew. Chem.* **1991**, *103*, 1706; *Angew. Chem. Int. Ed* **1991**, *30*, 1638; Heteropolyoxotungstates: c) X. Zuwei, Z. Ning, S. Yu, L. Kunlan, *Science* **2001**, *292*, 1139; d) K. Sato, M. Aoki, M. Ogawa, T. Hashimo, R. Noyori, *J. Org. Chem.* **1996**, *61*, 8310; e) C. Venturello, E. Alneri, M. Ricci, *J. Org. Chem.* **1983**, *48*, 3831; (TACN)Mn: f) C. Bolm, D. Kadereit, M. Valacchi, *Synlett* **1997**, *6*, 697; g) C. Bolm, S. M. Ceccarelli, A. Grenz, *Chem. Commun.* **2001**, 1726; h) A. Berkessel, C. A. Sklorz, *Tetrahedron Lett.* **1999**, *40*, 7965; i) D. De Vos, T. Bein, *Chem. Commun.* **1996**, 917; l) B. S. Lane, K. Burgess, *J. Am. Chem. Soc.* **2001**, *123*, 2934.

[151] Angelino Doppiu, planned Dissertation, RWTH, Aachen University;

[152] a) Corinne Pala, Dissertation, RWTH Aachen University; b) C. Kaulen, C. Pala, C. Hu, C. Ganter, *Organometallics* **2001**, *20*, 1614.

3.7.2 Iron as metal centre

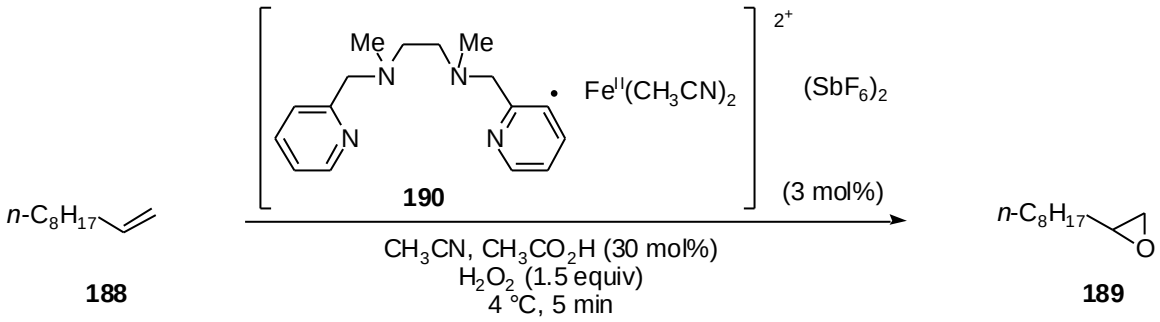
Iron is one of the most interesting metals in the periodic table as it is inexpensive, environmentally friendly and non-toxic. In combination with porphyrinic ligands, iron has been often used in catalytic oxidations.[153] Such systems are mimics of hemoglobine binding to oxygen in a reversible manner. By combinatorial screening of different metal percursors and polyamino acids supported on polystyrene, Francis and Jacobsen found that the combination reported in Scheme 53 is a new asymmetric system for the epoxidation of olefins with H_2O_2.[154]



Scheme 53 Iron catalyzed oxidation of olefins.

Moreover, Jacobsen recently reported the synthesis and catalytic activity of a MMO (methane monooxygenase) mimic system for the catalytic alkene epoxidation with aqueous hydrogen peroxide (Scheme 54).[155] The easily prepared iron-tetradentate ligand complex **187** was employed in combination with 1 equivalent of acetic acid, resulting in a catalytic system that assembled itself under the reaction conditions to form a μ-oxo, carboxylate-bridged diiron(II) complex. This catalyst acted efficiently in the epoxidation of a wide variety of aliphatic olefins, including terminal olefins, within 5 minutes and with high isolated yields.

[153] a) J. P. Collman, *Science* **1993**, *261*,1404; b) J. P. Collman, Z. Wang, A. Straumanis, M. Quelquejou, E. Rose, *J. Am. Chem. Soc.* **1999**, *121*, 460.
[154] M. B. Francis, E. N. Jacobsen, *Angew. Chem.* **1999**, *111*, 987; *Angew. Chem. Int. Ed.* **1999**, *38*, 937.
[155] M. C. White, A. G. Doyle, E. N. Jacobsen, *J. Am. Chem. Soc.* **2001**, *123*, 7194.



Scheme 54 MMO (methane monooxygenase) mimic system for the catalytic alkene epoxidation.

The activity of $Fe(ClO_4)_2$ was tested in the Baeyer-Villiger oxidation of prochiral 3-phenylcyclobutanone (**32**). At 0 °C full conversion to the lactone was observed with 0.1 equivalents of the iron salt and H_2O_2 as oxidant. When the reaction was run with $Fe(ClO_4)_2$ in combination with 2 equivalent of bipyridine as ligand, 30% conversion at room teperature and 100% conversion at 0 °C took place. Presumably, at room temperature the decomposition of the peroxide was too fast in the presence of iron cations, thereby decreasing the yield of the lactone. Some chiral ligands were also employed in order to investigate an asymmetric variant of this reaction. The nitrogen containing chelators used are shown below (Figure 12).

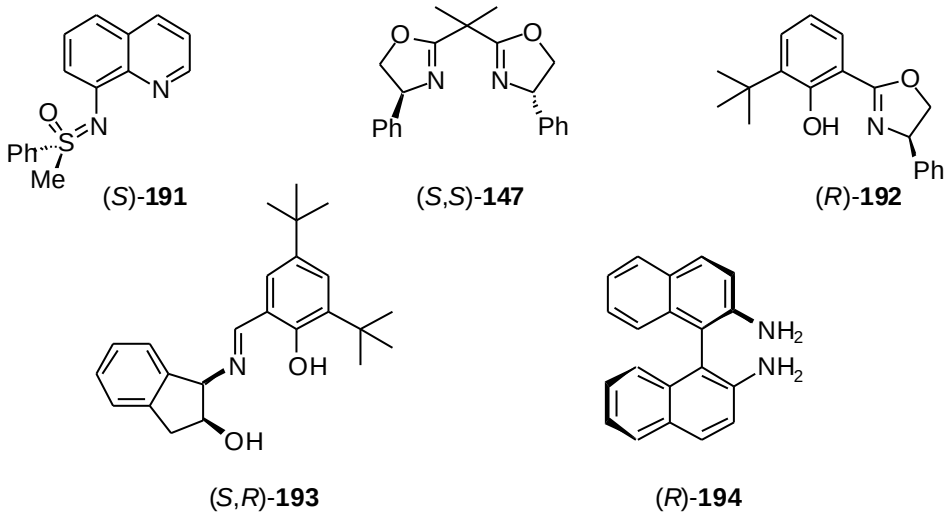
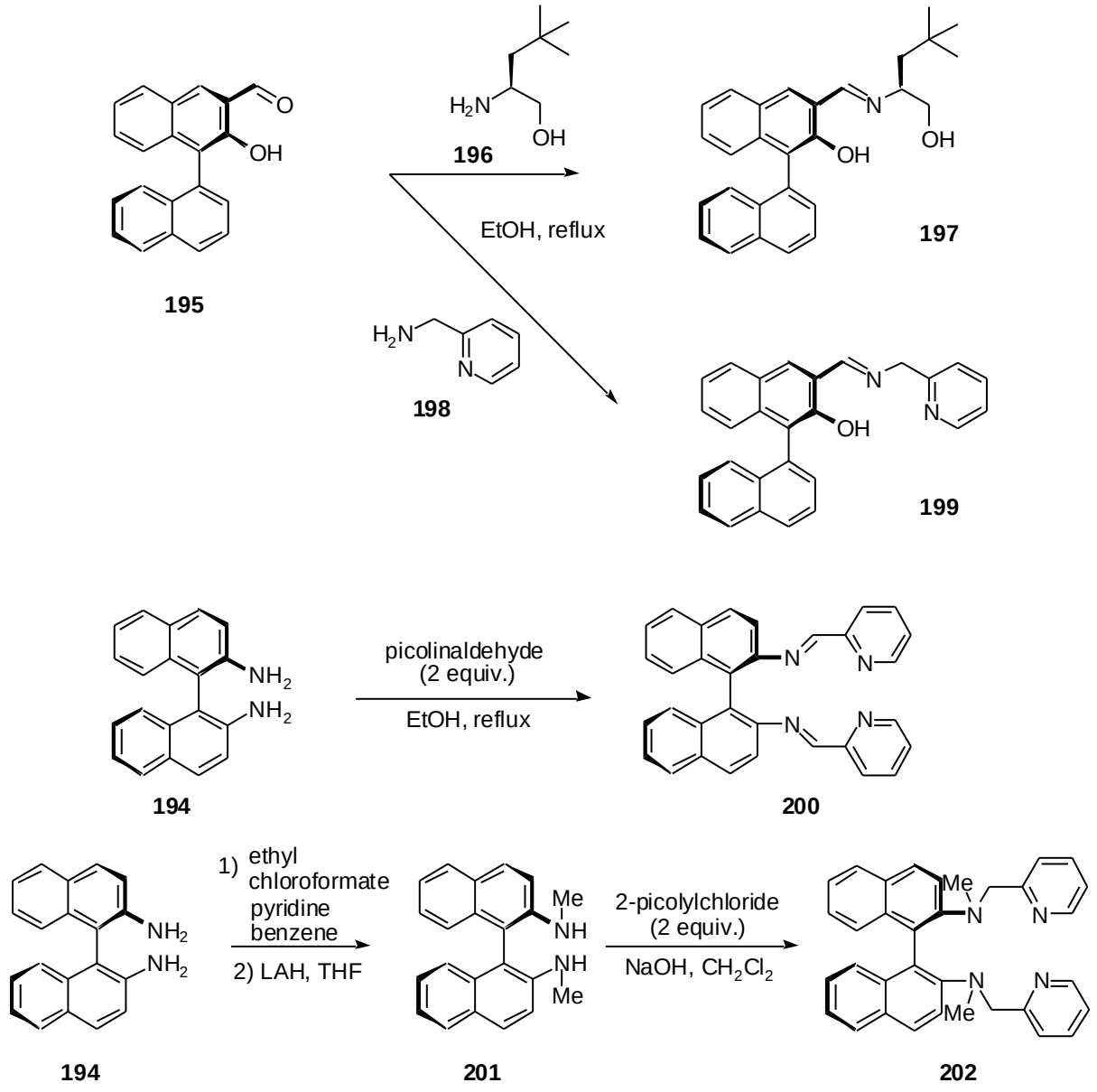


Figure 12 Chiral compounds used as ligands in the Fe-catalyzed Baeyer-Villiger oxidation.[156]

With all of these systems, racemic products were obtained.[157] As one explanation could be the labile bond between ligands and metal centre, some tetradendate ligands were synthesized in

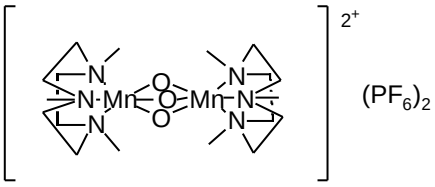
[156] For compound **191:** Marinella Verrucci, planned dissertation, RWTH, Aachen University.
[157] Reaction conditions in the Baeyer-Villiger oxidation: Ligand (0.02 mmol), $Fe(ClO_4)_2$ (0.02 mmol), solvent (2 mL), 3-phenylcyclobutanone (**32**) (0.2 mmol), H_2O_2 (0.5 mmol), 24 h, 0 °C to room temperature.

order to imitate the more stable porphyrinic catalysts. Starting from the enantiopure 2-hydroxy-[1,1']binaphthalenyl-3-carbaldehyde (**195**) through condensation with an amino alcohol or with 2-picolylamine, respectively, **197** and **198** were obtained (Scheme 55). Bisimine **200** was obtained by condensation of 1,1'-binaphthalenyl-2,2'-diamine (**194**, BINAM) with two equivalents of picolinaldehyde. Compound **202** was prepared, following the synthetic strategy used by Jacobsen for the synthesis of **190**, by first converting BINAM into the corresponding methylamine and then performing the reaction with 2-picolylchloride. All four compounds were tested in the Baeyer-Villiger reaction of cyclobutanone (**32**).[157] They all led to complete conversion to the lactone, yet could not provide any enantiomeric excess neither in methanol nor in acetonitrile as solvent.



Scheme 55 Synthesis of ligand precursors.

Various manganese-containing complexes have proved to be very successful in olefin epoxidation. Burgess has shown that 1 mol% of $MnSO_4$ was sufficent to oxidize cyclic or acyclic olefins in high yields using an excess of H_2O_2 (10 equivalents). The presence of additives was necessary, and the best one was found to be sodium bicarbonate. In this way, the solution had an optimum pH of 8.[150l] Jacobsen and Katzuki reported their well-known examples of asymmetric epoxidation with manganese salen catalysts for *cis*- or *trans*-olefins.[158] These catalysts are mainly active with oxidants such as NaOCl or PhIO but also with the Mukayiama system,[159] i.e. the combination of dioxygen and an aldehyde. Some improvements have been reported as regards oxidants and even variants with H_2O_2 have become known.[160] An alternative is, for instance, the use of 1,4,7-triazacyclononanes as ligands coordinated to manganese, a system intensively studied by Peacock and Wieghardt.[161]



203

Figure 13 Manganese/TMTACN-complex investigated by Wieghardt.

In Figure 13, one of the complexes characterized by Wieghardt is depicted, namely a triazacyclononane dimeric Mn μ^3-oxo complex. It has been employed in epoxidation reaction in combination with a stoichiometric amount of acetic acid, used as activator. Complex **203** seemed interesting as a potential catalyst in other oxidation reactions. Therefore, the Baeyer-Villiger oxidation of a cyclobutanone **32** and 2-phenylcyclohexanone, using compound **203** as catalyst, was tested under different conditions. The catalyses were performed in acetonitrile as solvent, with or without addition of acetic acid. Moreover, also the analogous complex

[158] a) W. Zhang, J. L. Loebach, S. R. Wilson, E. N. Jacobsen, *J. Am. Chem. Soc.* **1990**, *112*, 2801; b) R. Irie, K. Noda. Y. Ito, N. Matsumoto, T. Katsuki, *Tetrahedron Lett.* **1990**, *31*, 7345; c) E. N. Jacobsen in *Catalytic Asymmetric Synthesis*, (Ed.: J. Ojima), VCH **1993**, p 159; d) T. Katsuki, *Coord. Chem. Rev.* **1995**, *140*, 189; e) T. Katsuki, *J. Mol. Catal* **1996**, *113*, 87; f) K. Muniz-Fernandez, C. Bolm in *Transition Metals for Organic Synthesis* (Eds.: M. Beller, C. Bolm) Wiley VCH, **1998**, p 271.

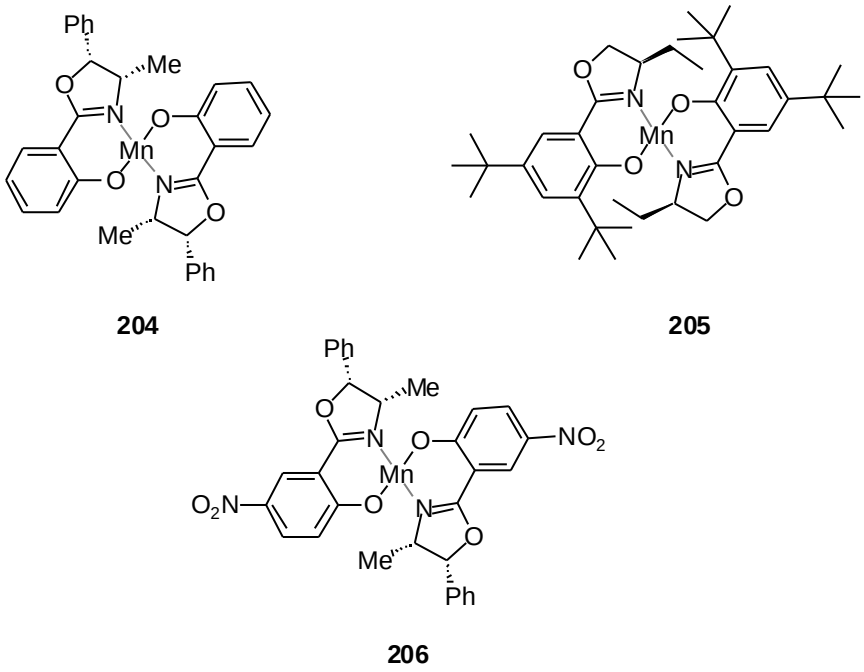
[159] T. Nagata, K. Imagawa, T. Yamada, T. Mukaiyama, *Inorg. Chim. Acta* **1994**, *220*, 283; b) T. Mukaiyama, *Chemm. Lett.* **1993**, 327; c) T. Mukaiyama, T. Yamada, T. Nagata, K. Imagawa, *Chemm. Lett.* **1994**, 1259; d) T. Mukaiyama, T. Yamada, *Bull. Chem. Soc. Jpn.* **1995**, *68*, 17; e) T. Mukaiyama, *Aldrichimica Acta* **1996**, *29*, 59.

[160] P. Pietikainen, *Tetrahedron* **1998**, *54*, 4319.

[161] A. A. Belal, P. Chaudhuri, I. Fallis, L. J. Farrugia, R. Hartung, N. M. Macdonald, B. Nuber, R. D. Peacock, J. Weiss, K. Wieghardt, *Inorg. Chem.* **1991**, *30*, 4397.

bearing carboxylato bridgeing groups was employed. It was immediatly evident that, even conducting the reaction at low temperature (+8 °C), extensive evolution of oxygen took place, due to the decomposition of hydrogen peroxide. Maybe it is this fast loss of oxidant in comparison to the high activation energy of the oxidation process, that led to a recovery of starting material even after 24 h of reaction time. Only in the oxidation of cyclobutanone **32** in the presence of acetic acid 13% conversion was detected

.



204 **205**

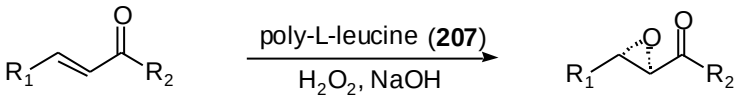
206

Figure 14 Manganese salox complexes.

Other chiral complexes bearing manganese as metal centre and bis-oxazol ligands (Figure 14) were also envisaged to be possible promotors for the Baeyer-Villiger oxidation with H_2O_2 but again no activity was observed.

3.7.3 Asymmetric Baeyer-Villiger oxidation without metals

Asymmetric catalysis without the use of metals is a field of chemistry that in the last years has found an ever increasing attention. Of course, the possibility to perform reactions without the need of expensive or toxic metals is especially interesting, in particular for industrial processes, such as the syntheses of pharmaceuticals or food additives. Several different approaches to this target have been published. One of the most remarkable in the field of oxidation chemistry is the Julia-Colonna epoxidation of enones (Scheme 56).[162] By employing a polyamino acid, namely poly-L-leucine (**207**), as catalyst and hydrogen peroxide as oxygen source, very good levels of enantioselection were reached. This outcome was attributed to the hydrogen-bond interaction of the substrate with the helical polyamino acid catalyst.



160 **161**

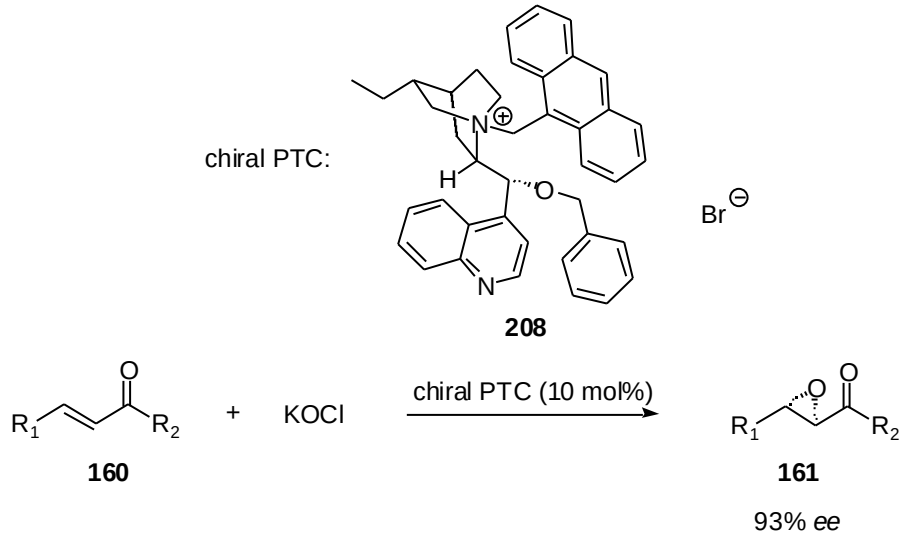
Scheme 56 Poly-L-leucine catalyzed oxidation of enones.

Organic phase transfer catalysts can also be effective tools for accelerating and controlling the regiochemistry and enantioselectivity of synthetic reactions. For example, the oxidation of α,β-enones **160** to form α,β-epoxy ketones **161** with H_2O_2 and sodium hydroxide in the presence of a benzylbromide salt of quinine as a chiral phase transfer catalyst has been intensively studied (Scheme 57).[163] Thanks to the pionieering work of Wynberg and co-workers and to the further modifications introduced by other groups, much progress has been made in tailoring of the ammonium salt which has resulted in a significant increase of

[162] Review: a) S. Ebrahim, M. Wills, *Tetrahedron: Asymmetry* **1997**, *8*, 3163; b) L. Pu, *Tetrahedron: Asymmetry* **1998**, *9*, 1457; c)J. V. Allen, S. M. Roberts, N. M. Williamson, *Adv. Biochem. Biotechnol.* **1998**, *63*, 125; d) S. Julia, J. Masana, J. C. Vega, *Angew. Chem.* **1980**, *92*, 968; *Angew. Chem. Int. Ed.* **1980**, *19*, 929; b) S. Julia,J. Guixer, J. Masana, J. Rocas, S. Colonna, R. Annunziata, H. Molinari, *J. Chem. Soc., Perkin Trans* **1982**, 1317; e) S. Colonna, H. Molinari, S. Banfi, S. Julia, J. Masana, A. Alvarez, *Tetrahedron* **1983**, *39*, 1635; f) S. Banfi, S. Colonna, H. Molinari, S. Julia, J. Guixer, *Tetrahedron* **1984**, *40*, 5207; g) P.A. Bentley, S. Bergeron, M. W. Cappi, D. E. Hibbs, M. B. Hursthouse, T. C. Nugent, R. Puludo, S. M. Roberts, L.E. Wu, *Chem. Comun.* **1997**, 739; h) W. Kroutil, P. Mayon, M. E. Lasterra-Sanchez, S. J. Maddrell, M. S. Roberts, S. R. Thornton, C. J. Todd, M. Tuter *Chem. Commun.* **1996**, 845.

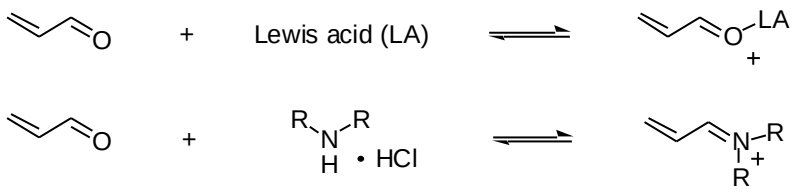
[163] a) R. Helder, J. C. Hummelen, R. W. P. M. Laane, J. S. Wiering, H. Wynberg, *Tetrahedron Lett.* **1976**, 1831; b) J. C. Hummelen, H. Wynberg, *Tetrahedron Lett.* **1978**, 1089; c) B. Marsman, H. Wynberg, *J. Org. Chem.* **1979**, *44*, 2312; d) H. Wynberg, B. Marsman, *J. Org. Chem.* **1980**, *45*, 158; e) B. Lygo, D. C. M. To, *Tetrahedron Lett.* **2001**, *42*, 1343; f) S. Arai, H. Tsuge, T. Shiori, *Tetrahedron Lett.* **1998**, *39*, 7563; g) E. J. Corey, F.-Y Zhang, *Org. Lett.* **1999**, *1*, 1287.

enantioselectivity of the products. Chiral quaternary chinchonidinium cations have found further applications in several other transformations.[164]



Scheme 57 Phase transfer catalysis.

A new strategy for organic catalysis consists in the use of chiral amines as enantioselective catalysts for a range of transformations that traditionally utilize metal salts.[165] The concept proposed by MacMillan is that a reversible formation of an iminium ion from the reaction of a α,β-unsaturated aldehyde and an amine might be similar to the activation of a carbonyl group by means of Lewis acid activation (Scheme 58).



Scheme 58 LUMO-lowering organocatalysis.

[164] a) E. J. Corey, F. Xu, M. C. Noe, *J. Am. Chem. Soc.* **1997**, *119*, 12414; b) E. J. Corey, Y. Bo, J. Busch-Petersen, *J. Am. Chem. Soc.* **1998**, *120*, 13000; c) E. J. Corey, M. C. Noe, F. Xu, *Tetrahedron Lett.* **1998**, *39*, 5347; d) M. Horikawa, J. Bush-Petersen, E. J. Corey, *Tetrahedron Lett.* **1999**, *40*, 3843; e) E. J. Corey, F.-Y. Zhang, *Angew. Chem.* **1999**, *111*, 2057; *Angew. Chem. Int. Ed.* **1999**, *38*, 1931.

[165] a) A. A. Kateri, J. B. Christopher, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 4243; b) W. S. Jen, J. J. M. Wiener, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2000**, *122*, 9874; c) H. Gröger, J. Wilken, *Angew. Chem.* **2001**, *113*, 545; *Angew. Chem. Int. Ed.* **2001**, *40*, 529; d) N. A. Paras, D. W. C. MacMillan, *J. Am. Chem. Soc.* **2001**, *123*, 4370; e) D. Enders, A. Seki, *Synlett* **2002**, 26; f) B. List, *J. Am. Chem. Soc.* **2000**, *122*, 9336; g) B. List, P. Pojarliev, C. Castello, *Org. Lett.* **2001**, *4*, 2001; h) K. Sakthivel, W. Notz, T. Bui, C. F. Barbas, *J. Am. Chem. Soc.* **2001**, *123*, 5260.

These systems are promising because they propose, in principle, alternative and efficient ways to various catalytic reactions. In this context, an important observation is that many of the systems used for enone epoxidation have turned out to behave as catalysts also in the Baeyer-Villiger oxidation. One could now assume that the activation of the carbonyl group involved in the Baeyer-Villiger oxygen insertion could be similar to the activation of the double bond of enones by means of carbonyl coordination. Therefore, metal free Baeyer-Villiger oxidations were attempted with bicyclooctanone **24** as model substrate. Poly-L-leucine (PLL) and sodium percarbonate and H_2O_2, respectively, in CH_3CN and CCl_4, however, did not affort any conversion. In contrast, with the combination of sodium percarbonate and THF as solvent full conversion was observed, yet with no enantiomeric excess.[166] Another metal free catalyst tried was (8*S*,9*R*)-*N*-benzylcinchonidinium chloride. The conversion to butyrolactone **33** remained modest (63%) when using lithium hydroxide and H_2O_2 in toluene.[167] Thus, this type of carbonyl group activation did not prove appropriate in the case of Baeyer-Villiger oxidation.

[166] Reaction conditions: PLL (40 mg) in 0.5 mL H_2O, cyclooctanone (**24**) (0.24 mmol), oxidant (0.36 mmol), solvent (0.5mL)

[167] Reaction conditions: (8*S*,9*R*)-*N*-benzylcinchonidinium chloride (0.02 mmol), LiOH (0.6 mmol), 3-phenylcyclobutanone (**32**) (0.2 mmol), H_2O_2 (0.2 mmol), toluene (1 mL)

3.8 Supercritical fluids

Supercritical is defined as the state of a compound, mixture or element above its critical pressure (p_c) and critical temperature (T_c). The properties of a supercritical fluid (SCF) are frequently described as being intermediate between those of a gas and a liquid. This is due to the fact that the gaseous and the liquid phase merge together and become indistinguishable at the critical point. However, this is not true for all properties. For example, compressibility and heat capacity are significantly higher near the critical point than they are in liquids or gases. A key feature of SCFs is that most of their properties show no discontinuity, in contrast to the conventional phases, which transform their physical state continuously. The schematic representation of the phase diagramme of pure carbon dioxide (Figure 15) shows the aggregation state of CO_2 as a function of pressure and temperature. The solid, liquid and gaseous states are separated by the melting, sublimation and evaporation curve, respectively. These three states are in equilibrium at the triple point. The critical point, on the other hand, marks the high temperature end of the evaporation line and is characterized by the critical temperature T_c = 31.1 °C and the critical pressure p_c = 73.8 bar. No distinct liquid or vapour phase can exist beyond the critical point, and the new supercritical phase has properties, which are reminiscent of both states. Supercritical carbon dioxide is CO_2 heated and pressurized beyond its critical point. Upon increasing pressure, supercritical CO_2 becomes more and more dense but never condenses into a liquid phase.

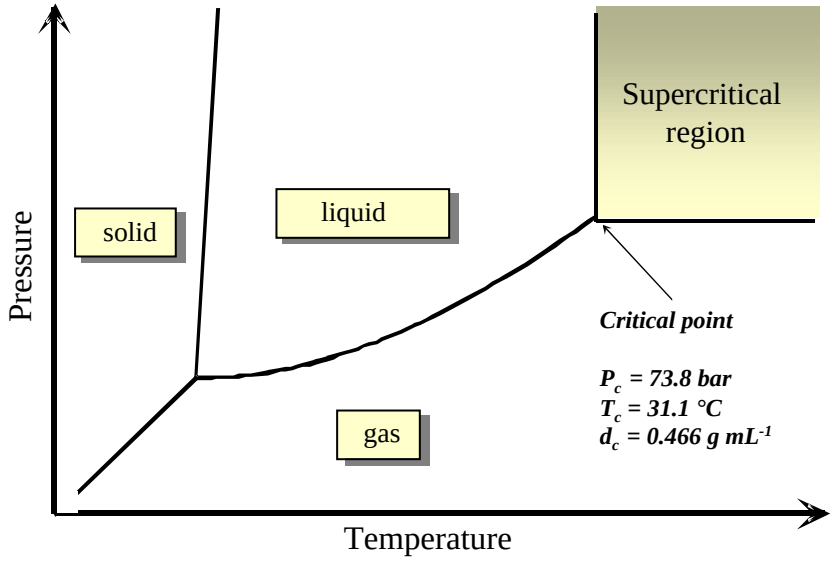


Figure 15 Phase diagramme of CO_2.

The supercritical phase diagramme refers only to a pure substance and cannot be used to represent a real chemical reaction system, which necessarily involves several components. In an experiment with several components dissolved in a solvent, one cannot ensure that the whole reaction mixture is in a single homogeneous phase merely by looking up the value of T_c of the pure solvent and then heating the vessel to that temperature. The actual critical parameters of the mixture may be substantially different from that of the pure solvent. Therefore, one can often only assume that the reaction vessel encompasses compressed CO_2 without specifying whether it is liquefied or already supercritical.

The physical properties of the supercritical phase are to some respect similar to the gas phase but also to the fluid phase (Table 18).[168] While the viscosity and the diffusivity are in the range of those of a gas, the density is more similar to that of a fluid. The density of a supercritical fluid close to the critical point is easily influenced by pressure and temperature changes.

Table 18 Comparison of some typical physical entities for gases, fluids and supercritical fluids.

Phase	Density [g cm^{-3}]	Diffusivity [cm^2 s^{-1}]	Viscosity [g cm^{-1} s^{-1}]
Gas	10^{-3}	10^{-1}	10^{-4}
Supercritical fluid	0.2 - 0.9	10^{-4} - 10^{-3}	10^{-4} - 10^{-3}
Liquid	1	$<10^{-5}$	10^{-2}

Diffusion coefficent and viscosity represent transport properties, which affect rates of mass transfer. In general, these properties are at least one order of magnitude higher or lower, respectively, compared with liquid solvents. This means that the diffusion of a species through a SCF medium will occur at a faster rate than in a liquid solvent, which implies that a solid will dissolve more rapidly in a SCF (if it is soluble). The most investigated supercritical

[168] U. van Wasen, I. Sweid, G. M. Schneider, *Angew. Chem.* **1980**, *92*, 585; *Angew. Chem. Int. Ed.* **1980**, *19*, 575; b) E. Dinjus, R. Fornika, M. Scholz, in *Chemistry under Extreme or Non-Classical Conditions* (Eds.: R. van Eldik, C. D. Hubbard), Wiley VCH, New York, **1996**, 219.

systems are carbon dioxide, ethane, ethylene and water.[169] The first three fluids have a critical temperature below 35° C while water in comparison with the other supercritical fluids has rather high critical data.

3.8.1 Applications of supercritical carbon dioxide

Supercritical carbon dioxide found its first application in food industry as solvent for separation processes, thanks to the pioneering work of Kurt Zosel at the Max-Planck-Institut für Kohlenforschung in Mülheim, Germany. Supercritical fluids extraction (SFE) using supercritical CO_2 is part of the current state of the art for the industrial production of decaffeinated coffee and of hops aroma. The interest for supercritical carbon dioxide as a solvent for organic reactions is grown only in the last decade. Especially due to reasons of environmental protection this reaction medium is becoming more and more important. CO_2 is advantageous because it is inexpensive, nonflammable, environmentally benign, and can be completely and easily removed from products. CO_2 is also naturally occurring and readily available; it can be found in natural reservoirs and is a by-product from the production of ammonia, ethanol, hydrogen and natural gases. Processes that use CO_2 do not add directly to the green house effect but rather aid in the reduction of emitted CO_2. Most of the CO_2 sold today is a by-product from other industries. Supercritical fluids are very attractive media for reactions because they offer the opportunity to manipulate the reaction environment, i.e. solvent properties, by varying the pressure to enhance the solubility of reactants and products and to eliminate interphase transport limitations on reaction rates. For all these reasons, they could be an environmentally benign substituent for some halogenated and aromatic solvents used in chemical syntheses.

Especially for oxidation reactions, safety considerations are undoubtedly a most convincing argument for the use of compressed CO_2 as a reaction medium. In fact, it is a priori non-flammable and non-oxidisable and acts as an efficient diluting agent raising the explosion limit so that even relatively high substrate and oxygen concentrations can safely be employed. Moreover, $scCO_2$ has a thermal capacity c_p much higher than a gas phase and, therefore, is predestinated for strong exothermic oxidation reactions.[170]

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[169] F. P. Lucien, N. R. Foster, in *Chemical Synthesis Using Supercritical Fluids* (Eds.: P. G. Jessop, W. Leitner), Wiley VCH, Weinheim, **1999**, 37.

[170] a) *CRC Handbook of Chemistry and Physic* (Eds.: D. R. Lide, H. P. R. Frederikse), CRC Press, BocaRaton, Florida, **1996**, 77; b) R. Span, W. Wagner, *J. Phys. Chem. Ref. Data* **1996**, *25*, 1509.

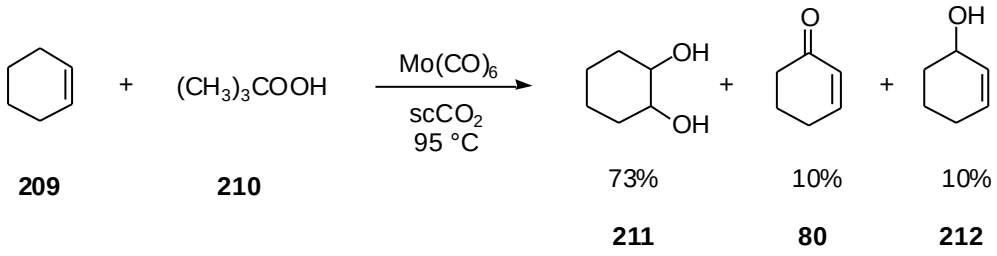
Table 19 Thermal capacity (c_p) of different reaction media

Reaction medium	Conditions	c_p [J g^{-1} K^{-1}]
gaseous CO_2	T = 27 °C, p = 1 bar, d(CO_2) = 1.77 10^{-3} g cm^{-3}	0.85
fluid CO_2	T = 25 °C, p = 64.1 bar, d(CO_2) = 0.71 g cm^{-3}	6.35
$scCO_2$	T = 57 °C, p = 200 bar, d(CO_2) = 0.74 g cm^{-3}	2.46
toluene	T = 25 °C	1.70
1,2-dichloroethane	T = 25 °C	1.30

Obviously, it is very important that the substrate is first diluted with the appropriate amount of CO_2 before oxygen is pressed into the mixture. Contact of the concentrated substrates with compressed oxygen can lead to formation of very explosive mixtures.

3.8.2 Oxidation reactions in supercritical carbon dioxide

Three groups have reported on the epoxidation of alkenes by hydroperoxides in $scCO_2$ in the presence of $Mo(CO)_6$. Noyori published the oxidation of 2,3-dimethylbutene by CHP in $scCO_2$ using as co-solvent tetrachloroethane.[171] Walther´s group found that cyclooctene reacts with TBHP in the presence of catalytic amounts of $Mo(CO)_6$ with complete selectivity to the corresponding epoxide.[172] Tumas et al. studied the oxidation of cyclohexene and allylic alcohols. In the first case (Scheme 59) by using a molybdenum catalyst, 73% of 1,2-cyclohexanediol was obtained, presumably from hydrolysis of the epoxide.

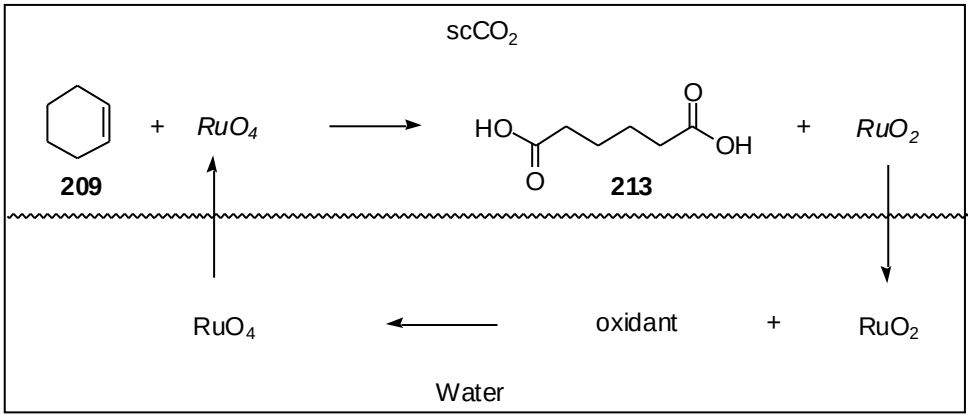


Scheme 59 Molybdenum catalyzed oxidation of cyclohexene.

[171] P. G. Jessop, *Top. Catal.* **1998**, *5*, 95.
[172] U. Kreher, S. Schebesta, D. Walther, *Anorg. Allg. Chem.* **1998**, *624*, 602.

In contrast complete conversion and 99% selectivity towards the epoxide was observed in the epoxidation of (*Z*)-non-3-ene-1-ol with $VO(OCH\text{-}(CH_3)_2)_3$.[173] An asymmetric version was devised by the same group reporting 87% *ee* in the epoxidation of (*E*)-hex-2-en-1-ol at 0 °C and therefore in liquid CO_2, by TBHP with Ti(*i*-OPr)$_4$ and diisopropyl-L-tartrate as catalyst system.[173]

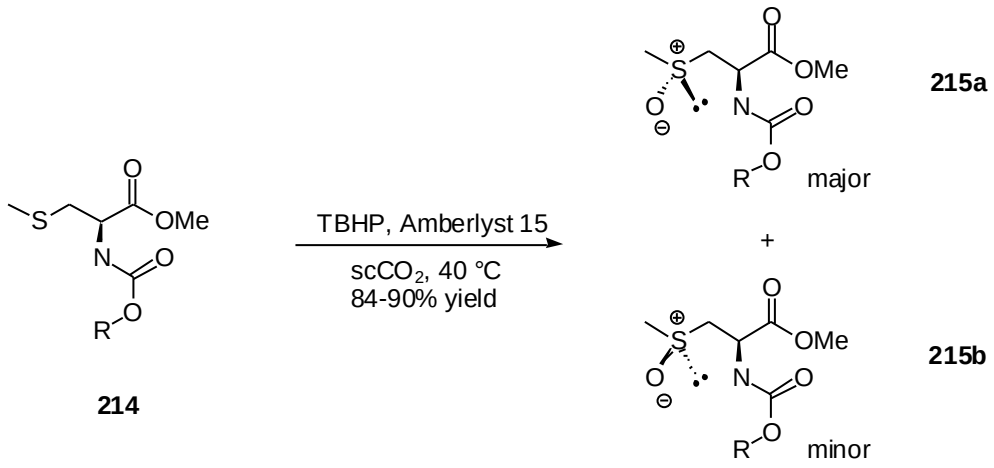
The catalytic oxidation of cyclohexene to adipic acid in a two phase system water/scCO_2 was also investigated by Tumas (Scheme 60). In this system the substrate and the product were soluble in the supercritical phase while the oxidant, $NaIO_4$, stayed in the aqueous one. The catalyst RuO_2 in water was oxidized to RuO_4, which acted as a phase transfer catalyst.[174] Unfortunately, rapid decomposition of the catalyst occurred.



Scheme 60 Catalytic oxidation in the two phase system water/scCO_2.

An interesting result was obtained by Rayner and co-workers in the sulfoxidation of chiral cysteine derivatives with TBHP using an Amberlyst 15 ion exchange resin in scCO_2.[175]

[173] D. R. Persiri, D. K. Morita, W. Glaze, W. Tumas, *Chem. Commun.* **1998**, 1015.
[174] D. A. Morgenstern, R. M. LeLacheur, D. K. Morita, S. L. Borkowski, S. Feng, G. H. Brown, L. Luan, M. F. Gross, M. J. Burk, W. Tumas in *Green Chemistry: Designing Chemistry for the Environment* (Eds: P. T. Anastas, T. C. Williamson) ACS: Washington DC, **1996**, Vol. 626, p 132.
[175] R. S. Oaches, A. A. Clifford, K. D. Bartle, M. T. Pett, C. M. Rayner, *Chem. Commun.* **1999**, 247.



Scheme 61 Sulfoxidation of a chiral cysteine derivative.

While no diasteroselectivity was observed in toluene or CH_2Cl_2, a dramatic pressure dependent increase in diasteroselectivity was found for $scCO_2$, the best results being achieved at 40 °C and 180 bar (Scheme 61). Until now there is no explanation of this effect.

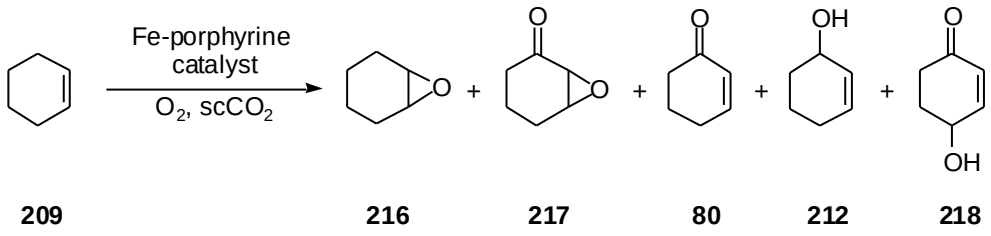
3.8.3 Aerobic oxidation in supercritical carbon dioxide

The use of molecular oxygen as primary oxidant represents a particularly attractive approach and at the same time a scientific challenge.[176] Supercritical CO_2 seems to be the ideal solvent for this kind of reactions because of its high miscibility with O_2. Potential problems associated with limited mass-transfer in conventional gas/liquid reaction systems can be circumvented by using supercritical carbon dioxide as solvent.

The first example of the combined use of $scCO_2$ and oxygen falls in the domain of enzymatic chemistry.[176c] Since enzymes are not soluble in $scCO_2$, these reactions are heterogeneous. Furthermore, the conditions must be optimized for each single system enzyme/substrate/$scCO_2$. However, it has been demonstrated that there are several enzymes which are stable in $scCO_2$ and that work for a relatively wide range of substrates.

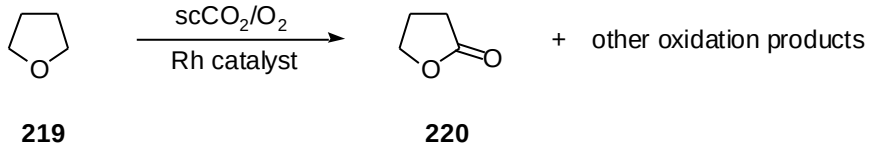
[176] a) R. A. Sheldon, J. M. Koki in *Metal Catalyzed Oxidation of Organic Compounds*, Academic press, New York, **1981**; b) K. A. Jørgensen, *Chem. Rev.* **1989**, *89*, 431; c) D. A. Hammond, M. Karel, A. M. Kalibanov, V. J. Krukonis, *Appl. Biochem. Biotech.* **1985**, *11*, 393.

The uncatalyzed oxidation of cyclohexane with oxygen to give cyclohexanone and cyclohexanol at 160 °C was reported by Srinivas but, here, only very low conversions were achieved (2% cyclohexanone and 0.6% cyclohexanol).[177] The group of Koda examined the same reaction but added 0.25 equivalent of acetaldehyde and used as catalyst an iron porphyrine system functionalized with pentafluorophenyl substituents in order to increase the solubility of the complex.[178] This time, at a temperature of 70 °C, 3% of the corresponding ketone and 2% of the alcohol were detected. The iron porphyrine-acetaldehyde system was also tried in the oxidation of cyclohexene (Scheme 62). Besides the epoxide, many by-products were formed due to radical allylic reactions.[179] The highest selectivity in the epoxide was 34% at 9% conversion.



Scheme 62 Oxidation of cyclohexene in $scCO_2$ catalyzed by iron porphyrine.

Another example of an oxidation in $scCO_2$ is the aerobic rhodium-catalyzed synthesis of γ-butyrolactone starting from tetrahydrofurane (Scheme 63).[180] Despite of the low solubility of the rhodium complex the oxidation to the lactone proceeded with a turnover number of 135, albeit with the formation of by-products.

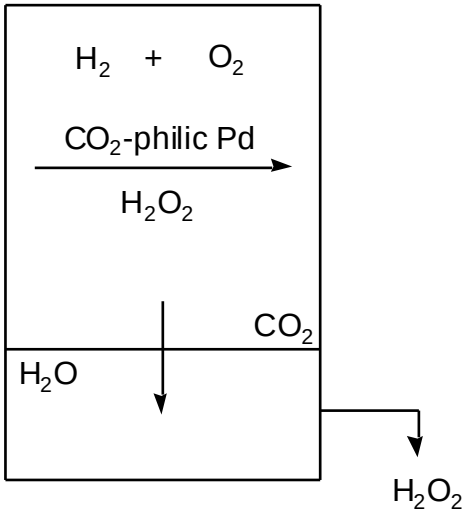


Scheme 63 Aerobic rhodium-catalyzed synthesis of γ-butyrolactone.

A very interesting contribution in the field of aerobic oxidation comes from Hancu and Beckman who proposed an alternative route for the synthesis of hydrogen peroxide based on

[177] P. Srinivas, M. Mukhopadhyay, *Ind. Eng. Chem. Res.* **1994**, *33*, 3118.
[178] X. W. Wu, Y. Oshima, S. Koda, *Chem. Lett.* **1997**, 1045.
[179] E. R. Birnbaum, R. M. Le Lacheur, A. C. Horton, W. Tumas, *J. Mol. Catal. A: Chem.* **1999**, *139*, 11.
[180] F. Loeker, D. Koch, W. Leitner, in *Selective Oxidations in Petrochemistry, DGMK-Tagungsbericht 9803* (Eds.: G. Emig, C. Kohlpaintner, B. Lücke), DGMK, Hamburg, **1998**, p. 209.

the catalyzed direct reaction of H_2 and O_2 in carbon dioxide as solvent (Scheme 64).[181] The current manufacture of this green oxidant is the AQ process, that is the sequential hydrogenation and oxidation of anthraquinone. This route does not have good credentials since it generates by-products, has a high energy demand and requires multiple unit operations.



Scheme 64 Alternative route for the synthesis of hydrogen peroxide.

Above 31 °C, H_2 and O_2 are miscible with CO_2 in all proportion and the palladium catalyst used by Beckman in the alternative synthesis is, due to the ligands, CO_2-philic. The hydrogen peroxide formed in the course of the reaction rapidly dissolves in the aqueous phase, minimizing the chances for product degradation through prolonged contact with the CO_2-soluble catalyst. The aqueous solution is furthermore stabilized by the CO_2 dissolved in water, which lowers the pH to 2.85.

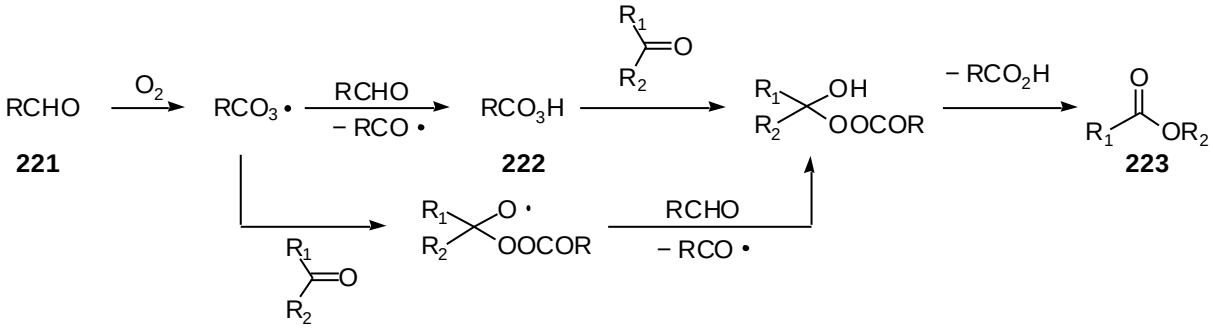
3.8.4 Baeyer-Villiger oxidation in compressed CO_2

The aerobic Baeyer-Villiger oxidation is generally carried out as a solution phase process with certain boundary conditions for the choice of the solvent. The solvent should possess high solubility for oxygen and organic substrates, it should be stable towards oxidation to avoid contamination by solvent degradation products, and it should be inflammable for safety reasons. Therefore, chlorinated solvents are generally preferred solvents for the Baeyer-

[181] D. Hancu, E. J. Beckman, *Green Chemistry* **2001**, *3*, 80.

Villiger oxidation despite the environmental and toxicological hazards connected with their use.

Kaneda and co-workers reported on the oxidation of various substituted cyclohexanones to ε-caprolactones with molecular oxygen and benzaldehyde at 40 °C in the absence of metal catalysts.[182] They found that addition of benzoyl chloride remarkably increased the yields of the Baeyer-Villiger oxidation products at a lower temperature of 20 °C. The most suitable solvent was carbon tetrachloride, 1,2-dichloroethane, ethyl acetate and benzene being good while alcohols and acetonitrile were poor solvents. In the case of substituted cyclohexanones, the Baeyer-Villiger reaction occurred regioselectively by means of migration of the more substituted carbon. Oxidation of cyclopentanone and norcamphor proceeded with slower rates but the higher activity of six membered ring ketones with perbenzoic acid had already been observed by Mateos and Menchaca.[183] Kaneda et al. suggested that the oxidation occurred by way of a peracid formed by autoxidation of the aldehyde. The mechanicistic pathway has also been described by Li et al. as follows:[184] an acylperoxy radical, which is the key intermediate in the autoxidation of aldehyde, is formed as the product of the reaction of benzaldehyde and oxygen (Scheme 65). The radical abstracts hydrogen from aldehyde to give peracid, which, in turn, reacts with the ketone to give a tetrahedral perhemiketal. Another pathway may occur as shown in Scheme 65, yielding the perhemiketal via a perhemiketyl radical. The tetrahedral intermediate would then undergo rearrangement to give ester or lactone.

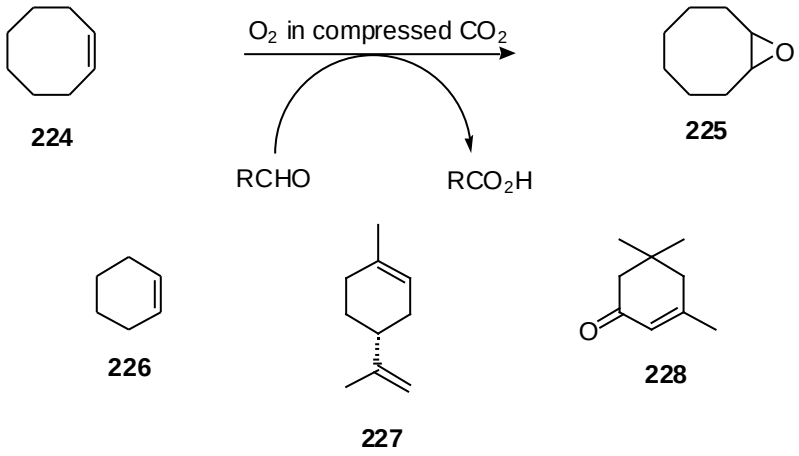


Scheme 65 Mechanicistic pathway for the aerobic oxidation in the presence of an aldehyde.

Various oxygen transfer reactions of this type occur under very mild reaction conditions in common organic solvents and in the presence of a metal catalyst (Mukaiyama conditions).

[182] K. Kaneda, S. Ueno, T. Imanaka, E. Shimotsuma, Y. Nishiyama, Y. Ishii, *J. Org. Chem.* **1994**, *59*, 2915.
[183] J. L. Mateos, H. Menchaca, *J. Org. Chem.* **1964**, *29*, 2026.
[184] X. Li, F. Wang, H. Zhang, C. Wang, G. Song, *Synth. Commun.* **1996**, *26*, 1613.

Recently, Leitner and co-workers used this Mukaiyama system for a catalyst-free, yet highly efficient epoxidation of olefins and oxidation of alkanes in compressed CO_2.[185] The stainless steel of the reactor wall was proposed to be responsible for the generation of an active oxidative species, most likely through its ability to promote the formation of acylperoxy radicals.



224 **225** **226** **227** **228**

conversion	95%	40%	16%
selectivity	91%	60% *cis*-1,2-epoxide 30% *trans*-1,2-epoxide 10% 8,9-epoxide	30%

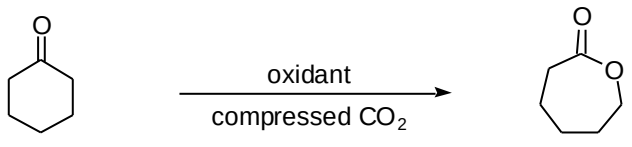
Scheme 66 Catalyst-free epoxidation of olefins.

Very good results were obtained under these conditions in the epoxidation reaction (Scheme 66): nearly quantitative conversion of *cis*-cyclooctene **224** and almost complete selectivity towards epoxycyclooctane **225** were observed. Epoxidation of the cyclic double bond was largely preferred over the attack at the terminal position. With linear olefins, epoxidation was almost quantitative in the case of *trans*-3-hexene containing an internal double bond and *trans*-3,4-epoxyhexane was formed as the only stereoisomer.

The issue to investigate at this point was whether also the Baeyer-Villiger oxidation would proceed in this unconventional sovent. The study was commenced by screening various

[185] (a) F. Loeker, W. Leitner, *Chem. Eur. J.* **2000**, *6*, 2011; (b) N. Theyssen, W. Leitner, *Chem. Commun.* **2002**, 410.

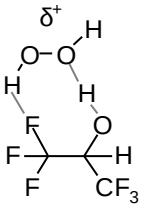
oxidants on their capability to selectively convert cyclohexanone **229** to caprolactone **230** in liquid or supercritical CO_2.



229 **230**

Scheme 67 Baeyer-Villiger oxidation in compressed CO_2.

Hydrogen peroxide (30% in water) alone remained ineffective as oxidant. Therefore, its activation by three routes was considered: (a) by the presence of a metal compound with hydroxy and hydroperoxy radicals being formed by a Haber-Weiss mechanism; (b) by the use of basic conditions to form the strong HOO^- nucleophile; or (c) by the in situ formation of percarboxylic acids. Basically, any compound able to reduce the electron density at the oxygen atom of hydrogen peroxide will facilitate nucleophilic attack and heterolytic oxygen transfer. Recently, Neumann published about electrophilic activation of hydrogen peroxide by means of perfluorinated solvents such as 1,1,1,3,3,3-hexafluoro-2-propanol in the absence of catalysts.[186,187] From ^1H and ^{17}O NMR spectra hydrogen bonds have been inferred. An electrophilically activated H_2O_2 is formed due to the strong electron-withdrawing properties of fluorine along with the hydrogen bond properties of the O−H hydrogen atom (Figure 16).



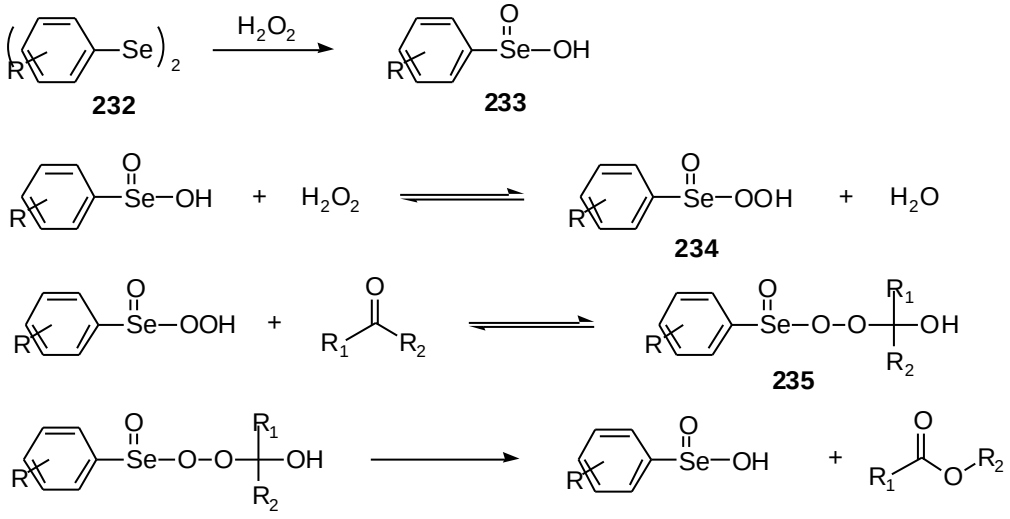
231

Figure 16 Electrophilic activation of hydrogen peroxide by means of perfluorinated solvents.

Thus, cyclic ketones were smoothly converted to lactones in high yields. Another approach towards the activation of H_2O_2 was recently reported by Sheldon and co-workers which

[186] K. Neimann, R. Neumann, *Org. Lett.* **2000**, *2*, 2861.
[187] For other reports on the peculiar properties of fluorinated solvents, see: a) M. C. A. van Viliet, I. W. C. E. Arends, R. A. Sheldon, *Chem. Commun.* **1999**, 821; b) M. C. A. van Viliet, I. W. C. E. Arends, R. A. Sheldon, *Chem. Commun.* **1999**, 263; c) T. M. Shryne, L. Kim, US Patent 4024165, **1977**.

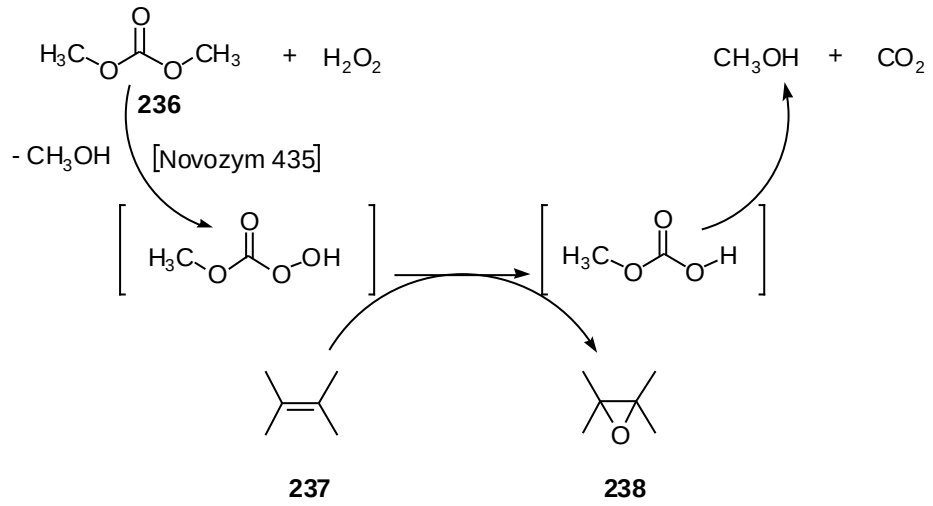
consisted in the use of fluoro-substituted diselenide compounds as catalysts in the fluorinated medium.[188] Benzene selenic acids represent one of the first catalysts for the Baeyer-Villiger oxidation with hydrogen peroxide.[189] The group of Sheldon developed a new version of this catalyst introducing a fluorine substituent on the benzyl ring. The mechanism for the reaction sequence is reported below in Scheme 68.



Scheme 68 Reaction sequence for the diselenide-catalyzed Baeyer-Villiger oxidation.

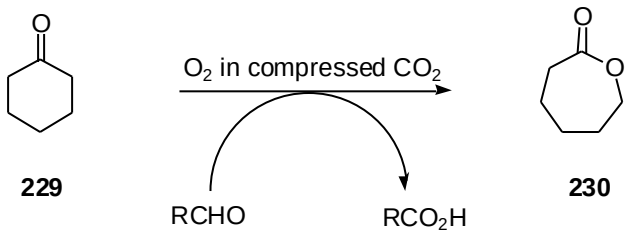
In the attempted Baeyer-Villiger oxidation of cyclohexanone, however, both addition of hexafluoro-2-propanol and of a catalytic amount of Ph_2Se_2 did not promote the oxidation reaction with hydrogen peroxide as oxidant and compressed CO_2 as solvent. Another interesting issue was the use of dimethylcarbonate as co-solvent, an idea stimulated by a work of Rüsch (Scheme 69).[190] By enzyme-catalyzed prehydrolysis of dimethylcarbonate with hydrogen peroxide, monoperoxy carbonic acid could be formed and used in situ for the Baeyer-Villiger oxidation of ketones. The co-product is unstable and decomposes to carbon dioxide and methanol. Dimethyl carbonate was added to the reaction mixture in CO_2 as potential activator but, unfortunately, this system remained inactive and no oxidation products were detected.

[188] G. J. Brink, J. M. Vis, I. W. C. E. Arends, R. A. Sheldon, *J. Org. Chem.*, **2001**, *66*, 2429.
[189] a) L. Syper, *Tetrahedron* **1987**, *43*, 2853; b) L. Syper, J. Mlochowski, *Tetrahedron* **1987**, *43*, 207; c) L. Syper, *Synthesis* **1989**, 167; d) H. Nishioka, K. Katsuno, M. Fujii, Y. Nishita, N. Koshiba, T. Narayama, *J. Pharm. Soc. Jpn.* **1999**, *119*, 519.
[190] M. Rüsch gen. Klaas, S. Warwel, *Org. Lett.* **1999**, *7*, 102.



Scheme 69 Epoxidation of alkenes by lipase-catalyzed perhydrolysis of dimethylcarbonate.

In contrast, the molecular oxygen/aldehyde combination led to high conversions even in the absence of any additives, affording the desired cyclic esters in good to excellent yields (Scheme 70).



Scheme 70 Mukaiyama´s system in the Baeyer-Villiger oxidation in compressed CO_2.

Among various commercially available aldehydes, benzaldehyde gave the best result leading to 75% conversion of the ketone under standard conditions (Table 20). Replacing the aldehydes with the corresponding acetals – a variation originally developed by Mukaiyama and co-workers for the epoxidation of acid sensitive olefins – did not result in the formation of caprolactone neither with dimethoxymethane nor propionaldehyde diethylacetal or benzaldehyde dimethylacetal.

Table 20 Screening of various oxidants.[a]

Entry	Oxidants	CO_2 [g]	T [°C]	t [h]	P [bar]	Conv.[b] [%]
1	actetaldehyde/O_2	9.3	20	20	86	67
2	pivaldehyde/O_2	9.7	27	21	90	70
3	benzaldehyde/O_2	9.7	22	21	90	75
4	dimethoxymethane/O_2	7.9	20	22	90	-
5	propionaldehyde diethylacetal/O_2	8.1	22	19	85	-
6	benzaldehyde dimethylacetal/O_2	8.9	23	20	80	-
7	H_2O_2	7	22	21	58	-
8	H_2O_2 + $(CH_3O)CO$	7.9	22	22	90	-

[a] For the reaction conditions see General Protocol GP6, Experimental Section.
[b] determined by GC.

The influence of the reaction conditions was investigated in more detail using cyclohexanone (**229**) and 3-*n*-octylcyclobutanone (**165**) as substrates and pivaldehyde as the co-reductant (Table 21). The amount of aldehyde had a major impact on the reaction course and high conversion required an aldehyde/substrate ratio of 3:1 (entries 2 and 5). As opposed to the amount of aldehyde, the partial oxygen pressure did not affect the oxidation significantly in the range of 5 - 30 bar (entries 1-3). The noticeable effect of the temperature partly reflects an intrinsic response of the reaction rates and partly the phase behaviour of the supercritical reaction medium. The rate of the aldehyde autoxidation increased more strongly with increasing temperature as compared to the Baeyer-Villiger process. Consequently, a larger excess of aldehyde was required to achieve similar ketone conversion at higher temperatures (entries 7 and 8). At the same time, the temperature increase resulted in the transition from a biphasic (liquid and gaseous CO_2) to a monophasic (supercritical) reaction mixture as confirmed by visual inspection. The resulting dilution of substrates over the whole reactor volume made the oxidation also less effective as demonstrated by dilution with liquid CO_2 at room temperature (entries 3 and 4).

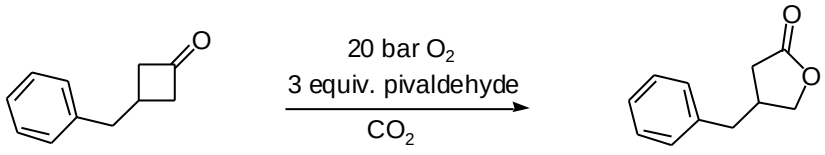
Table 21 Baeyer-Villiger reaction of cyclohexanone (**229**) and 3-*n*-octylcyclobutanone (**165**) in compressed CO_2 under different reaction conditions using pivaldehyde as co-reductant.[a]

Entry	Substrate	Aldehyde [eq.]	CO_2 [g]	pO_2 [bar]	T [°C]	Conv.[b] [%]
1	229	3	7.3	5	RT	71
2	229	3	7.4	20	RT	74
3	229	3	7.0	30	RT	70
4	229	3	15.1	20	RT	39
5	229	1.5	8.3	20	RT	41
6	165	3	9.0	20	RT	100
7	165	3	18.6	20	60	42
8	165	10	17.2	20	60	91

[a] For the reaction conditions see General Protocol GP6, Experimental Section.
[b] Determined by GC using *n*-decane as internal standard.

Similar observations were made in Baeyer-Villiger reactions of 3-benzyl-cyclobutanone (**166**) and bicycloctanone **24**. The oxidation reaction was performed at different temperatures between 35 °C and 85 °C (Table 22). Again, also in this case it was evident that a high temperature was detrimental to the conversion to the corresponding lactone.

Table 22 Baeyer-Villiger oxidation of 3-benzylcyclobutanone in compressed/sc CO_2

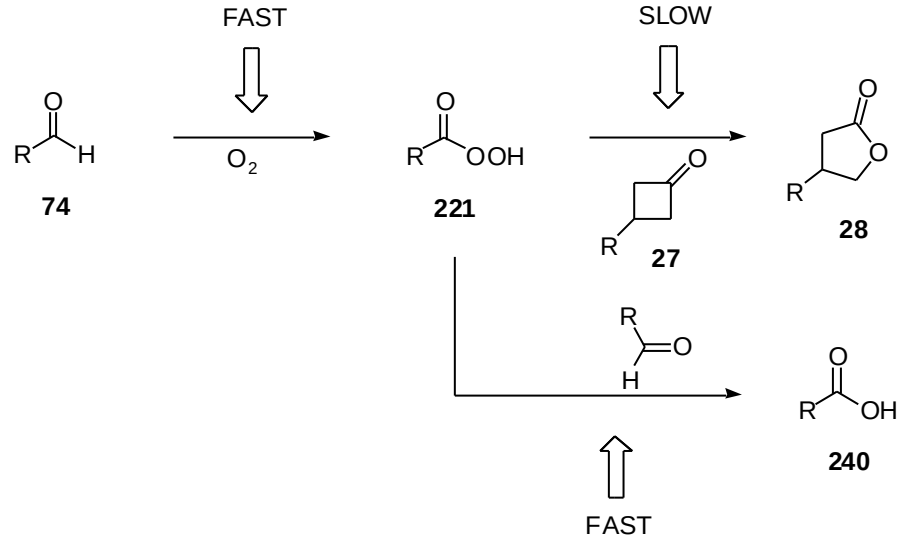


166 **239**

Entry	g CO_2	T [°C]	P [bar]	Conv. [%][a]
1	17.2	85	258	52
2	17.6	60	236	67
3	16	35	122	66

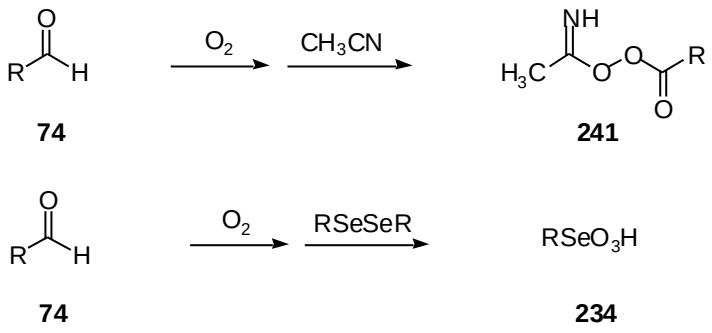
[a] For the reaction conditions see General Protocol GP6, Experimental Section.
[b] Determined by GC using *n*-decane as internal standard.

The reaction was also analyzed by means of an on-line gas chromatograph. The autoclave was directly connected with a GC and a sample of the reaction mixture was automatically injected every hour. In this way, it was possible to compare the decrease of aldehyde in the course of the reaction. A very fast consumption of aldehyde was observed while the oxygen insertion seemed to be a much slower process, as outlined in Scheme 71.



Scheme 71 Possible explanation of the mechanism of oxidation.

If this holds true, one could envisage as a remedy the activation of the ketone, for instance by adding a protonic acid such as tetrafluoroboronic acid, or activation of the oxidation step by adding acetonitrile that in some cases has proved to form very active oxidative species or a diselenide (Scheme 72). These additives could react, according to Scheme 72 with the peracid derivative.



Scheme 72 Other oxidants tried.

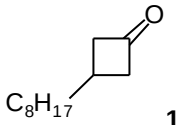
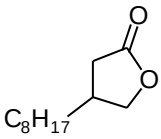
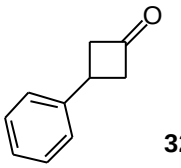
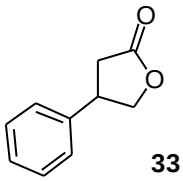
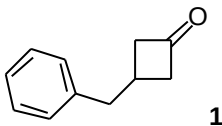
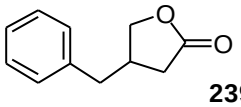
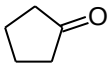
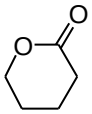
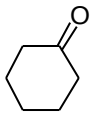
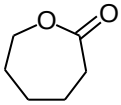
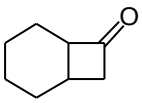
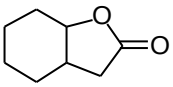
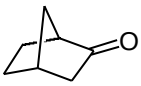
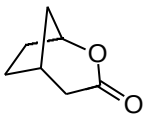
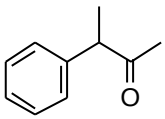
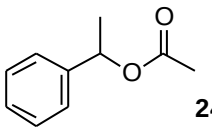
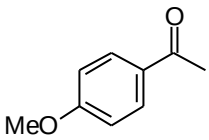
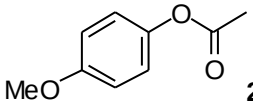
Addition of 1 mL of acetonitrile to the reaction mixture in the standard oxidation of cyclohexanone in compressed CO_2 at room temperature,[191] led to a decrease of conversion to 40%, while the use of a catalytic amount of Ph_2Se_2 (1 mol%) seemed not to affect the oxidation at all. Interestingly, 1 mL of perflorinated alcohol completely inhibited the Baeyer-Villiger oxidation of cyclohexanone. For further improvement of the conversions, Lewis acids were screened as catalysts for this oxidative transformation of ketones. Addition of catalytic amounts of $Cu(OAc)_2$ or $Sc(OTf)_3$ in the oxidation of cyclopentanone and cyclohexanone at room temperature did not afford any improvement but gave the same conversion.

In order to gain some mechanistic insight, the oxidation of cyclohexanone using pivaldehyde as co-reductant was monitored by on-line high pressure FT-IR spectroscopy. A few minutes after oxygen had been introduced, a new band grew in which can be assigned to 2,2-dimethyl-propionic peracid. Then, the ketone band disappeared with concomittant appearance of the band characteristic for pivalic acid. These data are consistent with a mechanism of the Baeyer-Villiger reaction involving the peracid as the active oxidant, whereas for epoxidation and alkane oxidation under similar conditions radical oxygen transfer processes have been implicated to prevail.

An intial assessment of the scope of the reaction under a standard set of reaction conditions demonstrated that a wide range of ketones, both cyclic and acyclic could be oxidized efficiently (Table 23). Various 3-substituted cyclobutanones were readily converted to their corresponding lactones in high yields (entries 1-3). Cyclopentanone (**50**) and cyclohexanone (**60**) reacted smoothly under these conditions giving δ- and γ-lactone, in 70% and 75% yield, respectively (entries 4 and 5). Larger rings, such as cycloheptanone and cyclooctanone, did not undergo ring expansion. The bicyclic ketones, bicyclo[4.2.0]octan-7-one (**24**) and bicyclo[2.2.1]heptan-2-one (**18**), were transformed readily into hexahydro-benzofuran-2-one (**25**) (entry 6) and 2-oxa-bicyclo[3.2.1]octan-3-one (**19**) (entry 7), respectively, following the expected regioselectivity. The acyclic substrates 3-phenyl-butan-2-one and p-methoxybenzophenone underwent oxidation, too, (entries 8 and 9), the higher conversion being obtained with the latter substrate. Also in these cases, the oxygen inserted exclusively into the C-C-bond between the carbonyl group and the most substituted carbon atom.

[191] According to the general procedure GP6, Experimental Section.

Table 23 Baeyer-Villiger oxidation with oxygen in compressed CO_2[a]

Entry	Substrate	Co-reductant	Products	Conv. [%][b]
1	 **165**	pivaldehyde	 **242**	100
2	 **32**	benzaldehyde	 **33**	82
3	 **166**	pivaldehyde	 **239**	75
4	 **50**	pivaldehyde	 **243**	70
5	 **229**	benzaldehyde	 **230**	75
6	 **24**	benzaldehyde	 **25**	64
7	 **18**	benzaldehyde	 **19**	92
8	 **244**	pivaldehyde	 **245**	48
9	 **246**	benzaldehyde	 **247**	79

[a] For the reaction conditions see general protocol GP6, Experimental Section.
[b] Determined by GC using *n*-decane as internal standard.

The Baeyer-Villiger oxidation of cyclohexanone **229** was run in conventional organic solvents under conditions comparable to those of Table 21 (entry 1). The O_2 pressure in these experiments was 5 bar and the reaction time was increased from 18 to 24 h. Two set of reaction were performed, with some steel shaving or without (Figure 17).

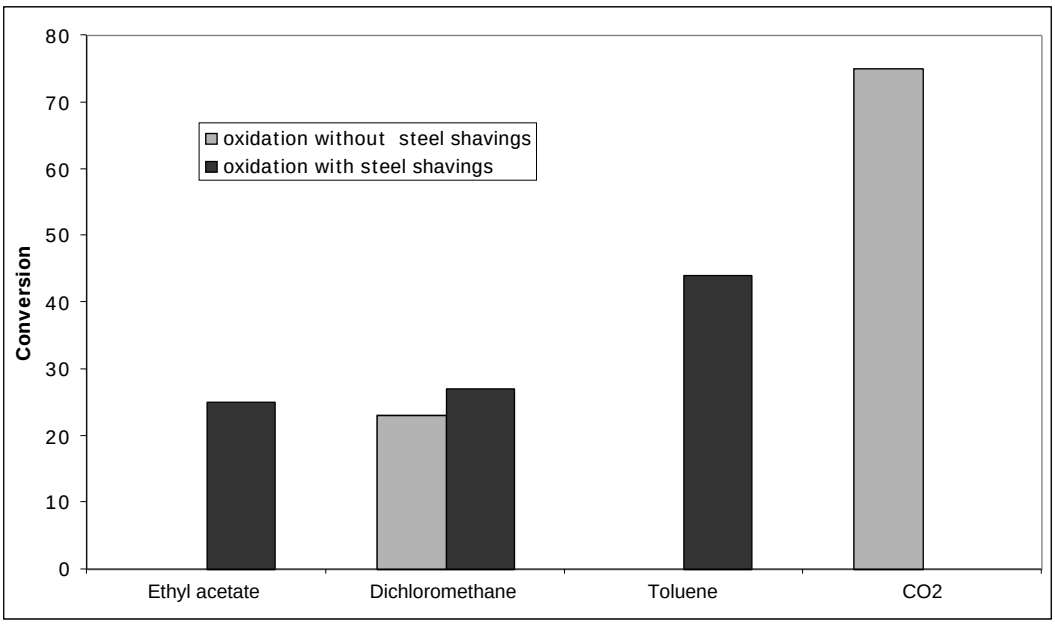


Figure 17 Aerobic Baeyer-Villiger oxidation: comparison with conventional solvents.

In the absence of steel, a modest conversion of 23% was achieved only in dichloromethane. In the presence of steel shavings, conversion was observed in all solvents, the best result being 44% conversion in toluene. The conversion increased in compressed carbon dioxide by a factor of 2.7 as compared to the standard solvent dichloromethane. This demonstrates that CO_2 is a greener replacement for CH_2Cl_2 providing significant advantages for the efficiency of the oxidation process.

In conclusion, it could be demonstrated that Baeyer-Villiger reactions can be performed very efficiently in compressed CO_2 at room temperature using oxygen as primary oxidant and an aldehyde as co-reductant. No additional catalyst is required and good to excellent yields were achieved for a wide range of cyclic (up to six-membered rings) and acyclic ketones. These results emphasize the large potential of compressed CO_2 as a benign and safe (“green”) reaction medium for oxidation processes in fine chemical synthesis.

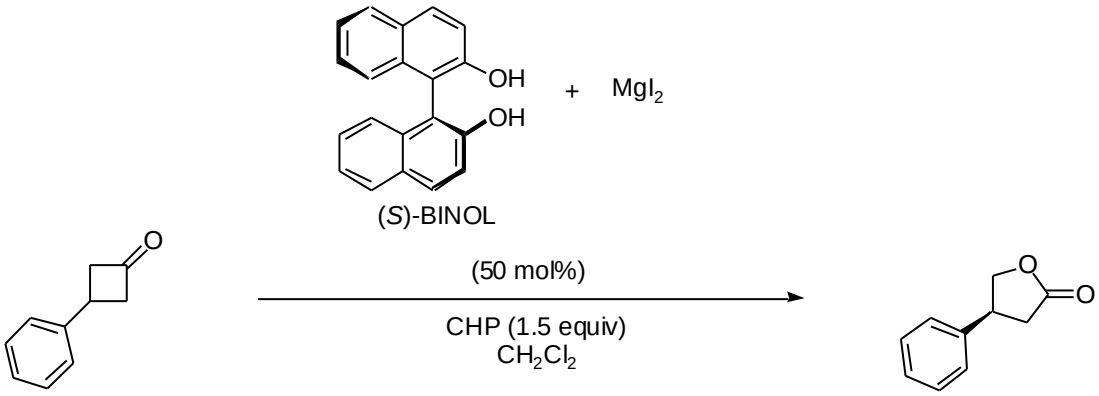
4 Summary

The following topics were dealt with in this thesis: First, the search for new efficient asymmetric versions of Baeyer-Villiger oxidations of cyclobutanones to γ-butyrolactones, and second, the development of a convenient oxidation system for the Baeyer-Villger reaction in supercritical CO_2.

One of the objectives of the present thesis was to improve the efficency of an aluminium-catalyzed Baeyer-Villiger oxidation which was recently discovered by Bolm and co-workers. The system is based on the combination of enantiopure 2,2′-dihydroxy-1,1′-binaphthyl (BINOL) and Me_2AlCl and utilizes a hydroperoxide as oxidant. A first attempt towards optimization consisted in the modification of the substitution pattern of the binaphthyl ligand. For this purpose, various substituted BINOL compounds were synthesized and applied in this asymmetric transformation, the focus being on 3,3'-substituted derivatives at first. Unfortunately and in contrast to many other catalyses reported in the literature that involve BINOL variants as ligands, this particular substitution of the binaphthyl scaffold proved to be detrimental to the enantioselection of the Baeyer-Villiger reaction. However, the introduction of electron-withdrawing groups, such as bromine and expecially trimethylsilylacetylene, in position 6 and 6' positions of the binaphthyl had a positive influence on the enantioselectivity, affording lactones with up to 81% *ee* at full conversion.

A further investigation was undertaken concerning the structure of the oxidant. While a general trend of the dependance of the enantiomeric excess of the products on the steric hindrance in the oxidizing agent could not be derived, the prevailing influence of the ligand was ascertained. Thus, the combination of either enantiomer of BINOL with (*S*)-1-phenylethyl hydroperoxide in enantiopure form showed that the ligand was responsible for the stereochemical configuration of the oxidation products. Modest co-operative effects between the chiral ligand and the chiral hydroperoxide as a result of matched and mismatched combinations were observed.

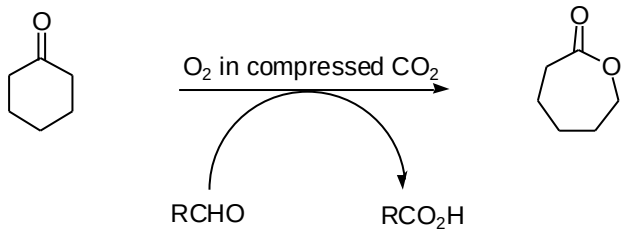
Moreover, a new asymmetric version of the Baeyer-Villiger reaction was devised. The combination of enantiopure BINOL and properly chosen magnesium reagents gave rise to species that were able to oxidize prochiral cyclobutanones to the corresponding butyrolactones in high yields and with modest to good enantioselectivity.



Scheme 73

It was discovered that with many magnesium reagents notable enantiomeric excesses were obtained. Among the various ones surveyed, MeMgI and MgI_2 afforded the best results, i.e. full conversion and *ee* values up to 60 and 65%, respectively.

Another goal of the present studies was the transfer of this oxidative transformation into compressed carbon dioxide as solvent.



Scheme 74

It was demonstrated that Baeyer-Villiger reactions can be performed very efficiently in compressed CO_2 at room temperature using the Mukaiyama system, i.e. oxygen as terminal oxidant and an aldehyde as co-reductant. A noticeable effect of the temperature was observed, which partly reflected an intrinsic response of the reaction rates and partly the phase behaviour of the reaction medium. At room temperature, the aldehyde autoxidation could be sufficiently suppressed to allow the oxidation of ketonic substrates to proceed. No additional catalyst was required and good to excellent conversions were achieved for a wide range of cyclic (up to C_6) and acyclic ketones. For instance, cyclohexanone and norbornan-2-one reacted smoothly giving the corresponding lactones in 75% and 92% conversion, respectively.

In conclusion, the Al-mediated asymmetric Baeyer-Villiger rearrangement could be further improved as regards to its enantioselectivity while with the magnesium-based catalysis a novel system for the enantioselective conversion of cyclobutanones to butyrolactones was developed. Additionally, aerobic Baeyer-Villiger oxidations were discovered to proceed in in the environmentally benign solvent carbon dioxide.

5 Experimental section

5.1 General methods and chemicals

5.1.1 Inert atmosphere conditions

All reactions involving air sensitive chemicals were carried out under argon atmosphere using standard Schlenk techniques.[192] Glassware were heated under vacuo and then streamed with argon. The addition of all reagents as well as solvents was carried out with glass or polypropylene syringes equipped with V2A steel needles under an argon stream. Labile chemicals were kept in the refrigerator (+2 °C or −25 °C) and/or stored under argon.

5.1.2 Solvents

The following solvents were dried and distilled under argon according to standard procedures:[193]

Dimethylsulfoxide:	dried over CaO, heated under reflux over CaH_2 in an argon atmosphere and finally subjected to fractionating distillation.
Pyridine:	heated under reflux over CaH_2, followed by distillation under argon.
Tetrahydrofurane:	heated under reflux over sodium/benzophenone ketyl radical, followed by distillation under argon.
Triethylamine:	heated under reflux over KOH, followed by distillation under argon; stored over KOH.
Acetonitrile:	distillation from calcium hydride.
Benzene:	distillation from sodium/benzophenone ketyl.
Dichloromethane:	distillation from calcium hydride.
Diethyl ether:	distillation from sodium/benzophenone ketyl.

The solvents for column chromatography, recrystallization and reaction work-up were distilled prior to use.

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

5.1.3 Determination of the physical data

^{1}H-NMR-Spectra:

^{1}H-NMR spectra were recorded at room temperature on a Varian VXR 300 (300 MHz), Gemini 300 (300 MHz), Inova 400 (400 MHz) or Unity 500 (500 MHz). Chemical shifts are given in ppm using tetramethylsilane (δ_H = 0.00 ppm) as internal standard. Coupling constants *J* are given in Hertz. Multiplicities: s (singulet), d (dublet), t (triplet), q (quartet), quin (quintet), m (multiplet), br (breit).

^{13}C-NMR-Spectra:

^{13}C-NMR spectra were ^{1}H-broad band-decoupled and measured with a Varian VXR 300 (75 MHz), Gemini 300 (75 MHz), Inova 400 (100 MHz) or Unity 500 (125 MHz). Chemical shifts are given in ppm using tetramethylsilane (δ_H = 0.00 ppm) as internal standard.

Melting point:

Melting points were determined on a Büchi B-540 and are uncorrected.

Optical rotation:

Optical rotation values were measured with a polarimeter Perkin-Elmer PE-241 (cuvette lengh *d* = 1.0002 dm; concentration *c* in 1 g/100 mL). The measurements were performed at a wavelengh of 589 nm (D-line of a sodium vapour lamp) and at room temperature. All values are uncorrected.

IR-spectroscopy:

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

Mass spectrometry:

Mass spectra were detected using a Varian (Varian MAT 212) spectrometer. All values are given in atomic units of mass per elemental charge (*m/z*). The intensity is given as a percentage of the base peak. Only signals of intensity > 20% are listed.

Thin layer chromatography (TLC):

TLC was performed using precoated aluminium backed sheets (Merck silica gel 60 F_{254}). The detection was performed by using UV radiation (λ = 254 nm) or developed with the following substances: 2.0 g of $KMnO_4$ and 5.0 g of K_2CO_3 in 100 mL of water (for ketones und lactones) or acidic cerium molybdate in methanol.

Column chromatography:

Separations by column chromatography were conducted according to the suggestions of Still.[194] Silica gel from Merck, Darmstadt, was employed as stationary phase (silica gel 60, mesh 40 - 63 µm). The ratios given for the eluating solvent mixture refer to the ratio of volumes of the eluents used.

Analytic HPLC:

For analyses by means of high performance liquid chromatography a HPLC system from Gynkotek was used:
autosampler GINA 50;
UV/VIS detector UVD 170S;
gradient pump M480G;
degasser DG 503.
The detection was performed at a wavelength of 254 nm. Stationary phases were chiral columns from Daicel Chemical Industries, Ltd. In order to ensure an inequivocal determination of enantiomeric excesses for each substance the respective racemate was separatedly measured as well. All chromatograms were baseline-separated.

[194] W. C. Still, M. Kahn, A. Mitra, *J. Org. Chem*. **1978**, *43*, 2923.

Gas chromatography:

Achiral gas chromatographic analyses were performed on a Hewlett-Packard 5890 Series II gas chromatograph equipped with a split mode injection system and a FID detector with mechanical pressure control. The stationary phase was an Ultra 2 column from Hewlett-Packard. Chiral gas chromatographic analyses for the determination of enantiomeric excesses were performed on a Hewlett-Packard 5890 Series II with and without electronic pressure control (EPC). In order to ensure an inequivocal determination of enantiomeric excesses for each substance the respective racemate was separatedly measured as well. All chromatograms were baseline-separated if not otherwise stated. The following chiral columns were applied:

Lipodex B: 2,6-dipentyl-3-acetyl-α-cyclodextrin (Macherey-Nagel GmbH & Co. KG);

Lipodex E: 2,6-dipentyl-3-butyryl-γ-cyclodextrin (Macherey-Nagel GmbH & Co. KG);

Lipodex G: octakis-(6-*O*-methyl-2,3-di-*O*-pentyl)-γ-cyclodextrin (Macherey-Nagel GmbH & Co. KG);

Cyclodex β-I/P: 2,3,6-trimethyl-β-cyclodextrin (Chromatographie Service GmbH).

Pre-columns used were FS-Phenyl-Sil columns (Chromatographie Service GmbH). The data acquisition and data integration were performed by a Hewlett-Packard ChemStation (Rev.A.05.04[273]) which was connected to the gas chromatographs via buffered HP-IB interfaces. When a pressure value is given in conjunction with a temperature value the pressure is to be considered as temperature dependant (EPC; constant flow). Otherwise the pressure given is meant to be a constant pressure on the column.

5.2 Synthesis of the substrates

5.2.1 Synthesis of monosubstituted, prochiral and bicyclic, racemic cyclobutanones

General protocol 1 (GP1 + GP2) for the synthesis of 3-monosubstituted and of bicyclic cyclobutanones:

a) Zinc-copper couple:[49a]

Zinc powder (63 g, 963 mmol) was shortly digerated with a 3% aqueous solution of HCl and decanted. The residue was washed with distillated water (4 × 50 mL) by digerating the suspension and subsequent decanting. Afterwards, one added a filtered 3% aqueous solution of $CuSO_4$, stirred the suspension, which became colourless, for 1 h and filtered it. The remainder was successively rinsed with acetone (4 × 125 mL) and MTBE (4 × 125 mL) and finally dried at 100 °C in vacuo for 24 h (storage under an argon atmosphere).

b) [2+2] Cycloaddition (GP1):[49b]

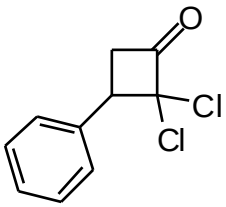
To a stirred suspension of Zn-Cu (2 eq.) and 120 mmol of an alkene in 240 mL dry diethyl ether was added dropwise, during 1 h at RT, a solution of phosphorus oxychloride (20.2 mL, 180 mmol) and trichloroacetyl chloride (16.5 mL, 180 mmol) in dry diethyl ether (100 mL). The suspension was refluxed for 2.5 h and finally stirred overnight. Then, the mixture was filtered through a pad of celite. The filtrate was concentrated to one third of the original volume under reduced pressure. Subsequently, the solution was washed with cold water, a saturated aqueous solution of $NaHCO_3$ and brine and dried over $MgSO_4$. After concentration under reduced pressure the crude product was used without further purification in the following dehalogenation step.

c) Dehalogenation (GP2):[49c,d]

To a stirred solution of the 2,2-dichloroketone in glacial acetic acid (0.6 M solution) was added Zn dust (4 eq.) and the suspension was stirred overnight at RT. The mixture was then diluted with diethyl ether and filtered. The solid was washed with diethyl ether and the combined organic extracts were diluted with toluene and concentrated under reduced pressure to one third of the volume. This operation of diluting and concentrating was repeated five times in order to co-evaporate the acetic acid. Afterwards, one diluted the residue with MTBE

(150 mL per 100 mmol starting material), washed it with a saturated aqueous solution of $NaHCO_3$ (2 × 50 mL) and with brine (each with the volume of the organic phase) and dried the organic phase over $MgSO_4$. The thus obtained crude product was purified by chromatography on silica gel or by distillation in vacuo. All the substrates were stored under an Ar atmosphere at +2°C.

5.2.1.1 *rac*-2,2-Dichloro-3-phenylcyclobutanone (*rac*-248)[49c,d]



Starting from styrene (12.5 g, 120 mmol), the product was synthesized according to the general procedure GP1.

19.35 g; yield = 75%

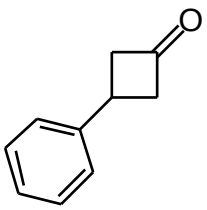
^{1}H-NMR (300 MHz, $CDCl_3$):

δ = 3.61 (dd, *J* = 53.3, 17.6 Hz, 1H), 3.65 (dd, *J* = 53.0, 17.6 Hz, 1H), 4.25 (t, *J* = 10.3 Hz, 1H), 7.28-7.47 (m, 5H).

^{13}C-NMR (75 MHz, $CDCl_3$):

δ = 45.7, 50.5, 89.6, 128.1, 128.4, 128.7. 134.5, 192.1.

5.2.1.2 3-Phenylcyclobutanone (32)[195,196]



Starting from *rac*-2,2-dichloro-3-phenylcyclobutanone (19.35 g, 90 mmol), the product was synthesized according to the general procedure GP2.

[195] E. V. Dehmlow, S. Büker, *Chem. Ber.* **1993**, *126*, 2759.
[196] G. Helmchen, G. Nill, *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 65.

7.9 g; yield = 60%

^{1}H-NMR (300 MHz, $CDCl_3$):

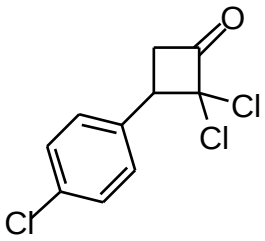
δ = 3.15-3.27 (m, 2H), 3.40-3.52 (m, 2H), 3.64 (quin, *J* = 8.2 Hz, 1H), 7.21-7.36 (m, 5H).

^{13}C-NMR (75 MHz, $CDCl_3$):

δ = 28.2, 54.5, 126.3, 126.5, 128.5, 143.4, 206.4.

GC: Lipodex B (25 m × 0.25 mm) with pre-column (3 m × 0.25 mm); 60 kPa N_2 at 140 °C; 140 °C, 15 min, 2 °C/min, 160 °C, 50 min; t_R = 15.8 min.

5.2.1.3 *rac*-2,2-Dichloro-3-(4′-chlorophenyl)-cyclobutanone (*rac* -249)[38f]



Starting from *p*-chlorostyrene (16.6 g, 120 mmol), the product was synthesized according to the general procedure GP1.

20.91 g; yield = 70%

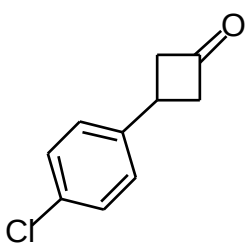
^{1}H-NMR (400 MHz, $CDCl_3$):

δ = 3.60 (dd, *J* = 48.6, 17.6 Hz, 1H), 3.63 (dd, *J* = 48.9, 17.6 Hz, 1H), 4.21 (t, *J* = 10.4 Hz, 1H), 7.23-7.26 (m, 2H), 7.39-7.42 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$):

δ =45.9, 50.0, 89.3, 128.8, 129.3, 132.8. 134.2, 192.3.

5.2.1.4 3-(4′-Chlorophenyl)-cyclobutanone (164) [38f]



Starting from *rac*-2,2-dichlor-3-(4′-chlorophenyl)-cyclobutanone (20.91 g, 84 mmol), the product was synthesized according to the general procedure GP2.

8.8 g; yield = 58%

^{1}H-NMR (400 MHz, $CDCl_3$):

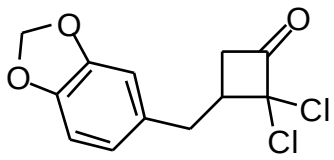
δ = 3.15-3.23 (m, 2H), 3.44-3.53 (m, 2H), 3.65 (quin, *J* = 8.8 Hz, 1H), 7.21-7.24 (m, 2H), 7.28- 7.31 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$):

δ = 27.9, 54.5, 127.7, 128.5, 132.1, 141.8, 205.6.

GC: Lipodex G (50 m × 0.25 mm) with pre-column (3 m × 0.25 mm); 100 kPa N_2 bei 160 °C; 160 °C isothermal; t_R = 41.3 min.

5.2.1.5 *rac*-2,2-Dichloro-3-(3′-4′-piperonyl)-cyclobutanone (*rac*-250)[197]



Starting from 1-allyl-3,4-(methylendioxy)-benzene (19.5 g, 120 mmol), the product was synthesized according to the general procedure GP1.

22.9 g; yield = 70%

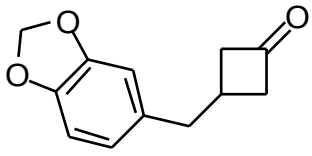
^{1}H-NMR (400 MHz, $CDCl_3$):

δ = 2.72 (dd, *J* = 14.3, 9.1, 1H), 3.01-3.08 (m, 1H), 3.11-3.19 (m, 1H), 3.22-3.19 (m, 2H) 5.95 (s, 2H), 6.66-6.78 (m, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$):

δ = 37.1, 47.4, 48.0, 88.5, 101.3, 108.7, 109.2, 121.9, 131.4, 146.7, 148.1, 192.6.

5.2.1.6 3-(3′-4′-Piperonyl)-cyclobutanone (90)[197]



Starting from *rac*-2,2-dichlor-3-(3′,4′-piperonyl)-cyclobutanone (17.76 g, 0.665 mol), the product was synthesized according to the general procedure GP2.

[197] M. Kuhn, A. von Wartburg, *Helv. Chim. Acta* **1967**, *50*, 1546.

8.63 g; yield = 65%

^{1}H-NMR (300 MHz, $CDCl_3$):

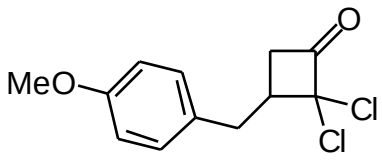
δ = 2.6-2.7 (m,1H), 2.71-2.82 (m, 4H), 3.06-3.14 (m, 2H), 5.92 (s, 2H), 6.61-6.75 (m, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$):

δ = 25.5, 41.9, 52.4, 101.1, 108.5, 109.1, 121.6, 133.9, 146.2, 147.9, 207.8.

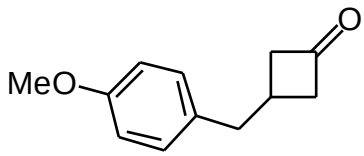
GC: Lipodex B (25 m × 0.25 mm) with pre-column (3 m × 0.25 mm); 80 kPa H_2 at 150 °C; 150 °C, 10 min, 5 °C/min, 170 °C, 120 min; t_R = 14.6 min.

5.2.1.7 *rac*-2,2-Dichloro-3-(4′-methoxy-benzyl)-cyclobutanone (*rac* -251)[198]



Starting from *p*-methoxystyrene (16.1 g, 120 mmol), the product was synthesized according to the general procedure GP1.

5.2.1.8 3-(4′-Methoxy-benzyl)-cyclobutanone (88)[198]



Starting from *rac*-2,2-dichloro-3-(4′-methoxy-benzyl)-cyclobutanone, the product was synthesized according to the general procedure GP2.

11.28 g; yield = 50%

^{1}H-NMR (400 MHz, $CDCl_3$):

δ = 2.53-2.61 (m, 1H), 2.63-2.70 (m, 2H), 2.74 (d, *J* = 7.4, 2H), 2.96-3.05 (m, 2H), 3.69 (s, 3H), 6.74-6.78 (m, 2H), 7.00-7.02 (m, 2H)

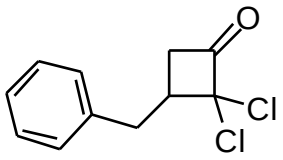
^{13}C-NMR (100 MHz, $CDCl_3$):

δ = 25.5, 41.3, 52.5, 55.5, 114.2, 129.7, 132.2, 158.3, 208.0.

[198] S. Shiotani, H. Okada, T. Yamamoto, K. Nakamata, J. Adaki, H. Nakamoto, *Heterocycles* **1996**, *43*, 113.

GC: Lipodex B (25 m × 0.25 mm) with pre-column (3 m × 0.25 mm); 80 kPa H_2 at 150 °C; 150 °C, 10 min, 5 °C/min, 170 °C, 120 min; t_R = 81.1 and 87.3 min.

5.2.1.9 *rac*-2,2-Dichloro-3-benzylcyclobutanone (*rac*-252)[195]



Starting from allyl-benzene (14.16 g, 120 mmol), the product was synthesized according to the general procedure GP1.

21.19 g; yield = 77%

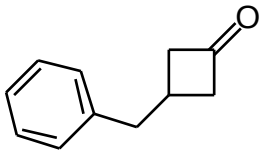
^{1}H-NMR (400 MHz, $CDCl_3$):

δ = 2.81 (dd, *J* = 9.3,14.2 Hz, 1H), 3.06 (dd, *J* = 8.2, 17 Hz, 1H), 3.17-3.37 (m, 3H), 7.20-7.36 (m, 5H)

^{13}C-NMR (100 MHz, $CDCl_3$):

δ = 37.5, 47.2, 48.1, 66.2, 127.1, 128.9, 129.0, 137.8, 192.7

5.2.1.10 3-Benzylcyclobutanone (166)[199]



Starting from *rac*-2,2-dichloro-3-benzylcyclobutanone (21.19 g, 92 mmol), the product was synthesized according to the general procedure GP2.

8.9 g; yield = 61%

^{1}H-NMR (300 MHz, $CDCl_3$):

δ = 2.68-2.84 (m, 3H), 2.87-2.93 (m, 2H), 3.07-3.18 (m, 2H), 7.16-7.25 (m, 3H), 7.28-7.34 (m, 2H).

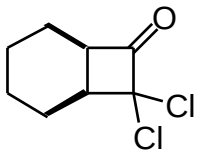
[199] K. Ogura, M. Yamashita, M. Suzuki, S. Furukawa, G. Tsuchinashi, *Bull. Chem. Soc. Jpn.* **1984**, *57*, 1637.

^{13}C-NMR (75 MHz, $CDCl_3$):

δ = 25.0, 41.8, 52.2, 126.3, 128.5, 128.5, 139.9, 207.9.

GC: Lipodex B (25 m × 0.25 mm); 60 kPa N_2; 170°C isothermal; t_R = 8.2 min.

5.2.1.11 *rac-cis*-8,8-Dichlorobicyclo[4.2.0]octan-7-one (*rac*-253)[49a]



Starting from cyclohexene (9.8 g, 120 mmol), the product was synthesized according to the general procedure GP1.

18.07 g; yield = 78%

^{1}H-NMR (400 MHz, $CDCl_3$):

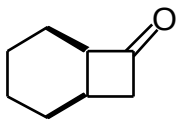
δ = 1.15-1.24 (m, 2H), 1.30-1.40 (m, 1H), 1.54-1.72 (m, 3H), 2.06-2.17 (m, 2H), 2.93-3.00 (m, 1H), 3.92-3.97 (m, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$):

δ = 20.6, 21.2, 21.5, 25.6, 43.1, 52.6, 87.8, 195.8.

GC: Lipodex B (25 m × 0.25 mm) with pre-column (3 m × 0.25 mm); 50 kPa N_2;
100 °C, 15 min, 1 °C/min, 160 °C, 15 min; t_R = 26.6 min.

5.2.1.12 *rac-cis*-Bicyclo[4.2.0]octan-7-one (*rac*-24)[49a]



Starting from *rac-cis*-8,8-dichlorobicyclo[4.2.0]octan-7-one (18.07 g, 94 mmol), the product was synthesized according to the general procedure GP2.

6.2 g; yield = 54%

^{1}H-NMR (400 MHz, $CDCl_3$):

δ = 1.04-1.26 (m, 3H), 1.39-1.48 (m, 1H), 1.52-1.59 (m, 2H), 1.94-1.98 (m, 1H), 2.13-2.19 (m, 1H), 2.44-2.50 (m, 2H), 3.11-3.18 (m, 1H), 3.26-3.30 (m, 1H).

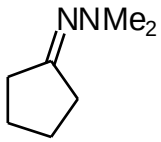
^{13}C-NMR (125 MHz, $CDCl_3$):

δ = 21.0, 22.2, 22.3, 22.4, 29.3, 52.0, 56.4, 209.7.

GC: Lipodex B (25 m × 0.25 mm) with pre-column (3 m × 0.25 mm); 60 kPa N_2; either 120 °C isothermal with t_R = 5.9 min or 120 °C, 2°C/min, 150 °C, 5 min with t_R = 4.9 min.

5.2.2 Synthesis of racemic 2-alkyl cyclic ketones

5.2.2.1 Cyclopentanone *N*,*N*-dimethylhydrazone (51)[50]



In a flask equipped with a Dean-Stark apparatus to remove water, a mixture of cyclopentanone (13.42 mL, 150 mmol), *N*,*N*-dimethylhydrazine (180 mmol, 13.68 mL), trifluoroacetic acid (0.075 mL), and benzene (60 mL) was added. The raection mixture was heated under reflux for 5 h and then cooled to room temperature. The content of the flask was diluted with diethyl ether (150 mL) and water (40 mL) and the organic layer was washed with brine and finally dried over $MgSO_4$. The filtrate was eventually concentrated under reduced pressure, and the residue was purified by distillation under reduced pressure.

15.71 g; yield = 91%

bp 58 °C/17 mmHg;

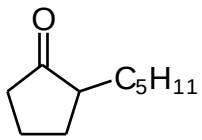
^{1}H-NMR (400 MHz, $CDCl_3$):

δ = 1.70-1.81 (m, 4H), 2.37-2.45 (m, 4H), 2.53 (s, 6H);

^{13}C-NMR (75 MHz, $CDCl_3$):

δ = 24.3, 25.0, 29.4, 33.6, 47.1, 175.5

5.2.2.2 *rac*-2-*n*-Pentylcyclopentanone (29)[50]



To a solution of cyclopentanone *N*,*N*-dimethylhydrazone (3 g, 26 mmol) in THF (20 mL) was added *n*-BuLi in hexane (27 mmol, 17.2 mL, 1.6 M in hexane) at -5 °C under an argon atmosphere. After the mixture had been stirred for 1 h at this temperature, pentyl bromide (27 mmol) was added, and stirring was continued for 20 h at room temperature. To the reaction mixture was then given 2 N aqueous HCl (20 mL). After stirring for one further hour, the mixture was extracted with EtOAc (3 x 20 mL). The organic layer was washed with water and brine and dried over $MgSO_4$. Finally, the crude product was purified by column chromatography (hexane:EtOAc = 6-12:1).

19.2 g; yield = 86%

^{1}H-NMR (300 MHz, $CDCl_3$):

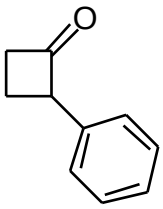
δ = 0.88 (t, *J* = 6.8 Hz, 3H), 1.19- 1.36 (br, 7H), 1.47-1.57 (m, 1H), 1.71-1.83 (m, 2H), 1.96-2.06 m, 2H), 2.08-2.15 (m, 1H), 2.17-2.34 (m, 2H)

^{13}C-NMR (75 MHz, $CDCl_3$):

δ = 14.0, 20.8, 22.5, 27.2, 29.6, 31.8, 38.1, 49.1, 60.3, 221.

GC: Ultra-2 (25 m × 0.2 mm × 0.33 μm); 50 kPa N_2; 100 °C, 5 min, 30 °C/min, 250 °C, 5 min, 30 °C/min, 300 °C, 15 min; t_R = 9.14 min.

5.2.3 *rac*-2-phenyl cyclobutanone (57)[51]



To a stirring solution of cyclopropylsulfonium tetrafluoroborate (1.5 g, 4.8 mmol) and benzaldehyde (371 mg, 3.5 mmol) in of dry dimethylsulfoxide (11 mL) at room temperature, powdered potassium hydroxide (392 mg, 7 mmol) was added in one portion and stirred for

additional 30 minutes. The reaction mixture was then poured onto cold aqueous 1 M tetrafluoroboric acid (8 mL) and extracted with diethylether (2 x 20 mL). The organic solution was washed with water, then dried over sodium sulfate and after evaporation of the solvent under reduced pressure, the residue (a mixture of diphenylsulfide and product) was purified by column chromatography (pentane: MTBE = 5 : 1) to obtain 300 mg of product as light yellow crystals.

300 mg; yield = 58%

^{1}H-NMR (300 MHz, $CDCl_3$):

δ = 2.18-2.26 (m, 1H), 2.47-2.55 (m, 1H), 2.97-3.04 (m, 1H), 3.16-3.22 (m, 1H), 4.49-4.55 (m, 1H), 7.22-7.33 (m, 5H).

^{13}C-NMR (75 MHz, $CDCl_3$):

δ = 17.9, 44.9, 64.7, 127.1, 128.8, 136.7, 207.6.

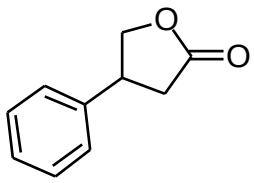
GC: Ultra-2 (25 m × 0.2 mm × 0.33 μm); 50 kPa N_2; 100°C, 5 min, 30°C/min, 250°C, 5 min, 30°C/min, 300°C, 15 min; t_R = 9.74 min.

Lipodex β-I/P (25 m × 0.25 mm) with pre-column (3 m × 0.25 mm); 100 kPa N_2; 140 °C isothermal with t_R = 21.7 min.

5.3 General protocol 3 (GP3): Racemic lactones obtained by Baeyer-Villiger oxidation with MCPBA

To an ice-cooled solution of the ketone (5 mmol) in dichloromethane (50 mL), $NaHCO_3$ (460 mg, 5.5 mmol) and *m*-chloroperbenzoic acid (1.23 g, 75% in water, 5.5 mmol) were added. The reaction mixture was then stirred at RT until conversion was complete (checked by TLC) before it was diluted with dichloromethane (600 mL). It was then washed with both a saturated aqueous solution of $NaHCO_3$ and brine and dried over $MgSO_4$. Finally, the solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel.

5.3.1 *rac*-4-Phenyltetrahydro-2-furanone (*rac*-33)[196]



Starting from 3-phenylcyclobutanone (731 mg, 5 mmol), the product was synthesized according to the general procedure GP3.

648 mg; yield = 80%

^{1}H-NMR (400 MHz, $CDCl_3$):

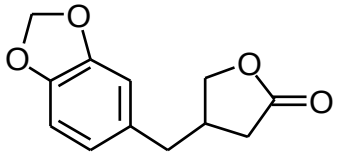
δ = 2.65 (dd, *J* = 17.3, 9.1 Hz, 1H), 2.90 (dd, *J* = 17.3, 8.5 Hz, 1H) 3.78 (quin, *J* = 8.2 Hz, 1H), 4.24 (t, *J* = 8.6 Hz, 1H), 4.64 (t, *J* = 8.5 Hz, 1H), 7.21-7.24 (m, 2H), 7.26-7.31 (m, 1H), 7.34-7.38 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$):

δ = 35.5, 40.9, 73.8, 126.5, 127.4, 128.8, 139.2, 176.1.

GC: Lipodex B (25 m × 0.25 mm) with pre-column (3 m × 0.25 mm); 60 kPa N_2 at 140 °C; 140 °C, 15 min, 2 °C/min, 160 °C, 50 min; t_R = 65.0 min [(+)-(*S*)] and 66.6 min [(−)-(*R*)].

5.3.2 *rac*-4-(3′,4′-Piperonyl)-tetrahydro-2-furanone (*rac*-91)[197]



Starting from 3-(3',4'-piperonyl)cyclobutanone (1.02 g, 5 mmol), the product was synthesized according to the general procedure GP3.

935 mg; yield = 85%

^{1}H-NMR (300 MHz, $CDCl_3$):

δ =2.27 (dd, *J* = 17.3, 7.2 Hz,1H), 2.59 (dd, *J* = 17.3, 8.0 Hz, 1H) 2.65-2.72 (m, 2H), 2.73-2.83 (m, 1H), 4.01 (dd, *J* = 9.3, 6.0 Hz, 1H), 4.32 (dd, *J* = 9.3, 7.2 Hz, 1H), 5.94 (s, 2H), 6.59-6.64 (m, 2H), 6.75 (d, *J* = 8 Hz, 1H)

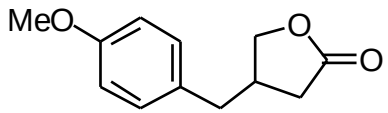
^{13}C-NMR (100 MHz, $CDCl_3$):

δ =34.5, 37.6, 38.9, 72.8, 101.3, 108.7, 109.1, 121.9, 132.1, 146.6, 148.1, 176.9.

GC: Ultra-2 (25 m × 0.2 mm × 0.33 μm); 50 kPa N_2; 100 °C, 5 min, 30 °C/min, 250 °C, 5 min, 30 °C/min, 300 °C, 15 min; t_R = 11.4 min.

Lipodex B (25 m × 0.25 mm) with pre-column (3 m × 0.25 mm); 100 kPa H_2 at 170 °C; isothermal 170 °C, 230 min; t_R = 166.0 and 182.3 min.

5.3.3 *rac*-3-(4′-Methoxy-benzyl)- tetrahydro-2-furanone (*rac*-89)[198]



Starting from (951 mg, 5 mmol), the product was synthesized according to the general procedure GP3.

814 mg; yield = 79%

^{1}H-NMR (400 MHz, $CDCl_3$):

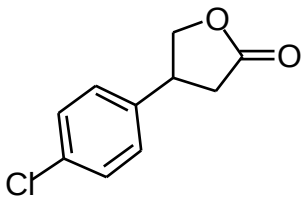
δ = 2.30 (dd, *J* = 17.3, 6.8 Hz,1H), 2.62 (dd, *J* = 17.3, 8.0 Hz,1H), 2.70-2.73 (m, 2H), 2.76-2.85 (m, 1H) 3.80 (s, 3H), 4.40 (dd, *J* = 9.1, 6.0 Hz, 1H), 4.70 (dd, *J* = 9.1, 6.9 Hz, 1H), 6.83-6.87 (m, 2H), 7.05-7.09 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$):

δ = 34.5, 37.7, 38.4, 55.6, 72.9, 114.4, 129.8, 130.4, 158.6, 177.1.

GC: Ultra-2 (25 m × 0.2 mm × 0.33 μm); 50 kPa N_2; 100 °C, 5 min, 30 °C/min, 250 °C, 5 min, 30 °C/min, 300 °C, 15 min; t_R = 18.3 min.

5.3.4 *rac*-4-(4′-Chlorophenyl)-dihydrofuran-2-one (*rac*-254)[200]



Starting from (903 mg, 5 mmol), the product was synthesized according to the general procedure GP3.

747 mg; yield = 76%

^{1}H-NMR (400 MHz, $CDCl_3$):

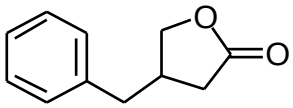
δ = 2.63 (dd, *J* = 17.3, 8.8 Hz, 1H), 2.93 (dd, *J* = 17.6, 8.8 Hz, 1H) 3.78 (quin, *J* = 8.5 Hz, 1H), 4.23 (dd, *J* = 9.1, 7.7 Hz, 1H), 4.66 (dd, *J* = 9.3, 8.0 Hz, 1H), 7.16-7.20 (m, 2H), 7.33-7.36 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$):

δ = 35.6, 40.5, 73.7, 127.9, 129.1, 133.4, 137.8, 175.8.

GC: Lipodex G (50 m × 0.25 mm) with pre-column (3 m × 0.25 mm); 100 kPa N_2 at 160 °C; 160 °C; t_R = 163.0 and 166.1 min.

5.3.5 *rac*-4-Benzyldihydrofuran-2-one (*rac*-239)[201]



Starting from (800 mg, 5 mmol), the product was synthesized according to the general procedure GP3.

572.6 mg; yield = 65%

[200] J. W. Lawston, T. D. Inch, *J. Chem. Soc., Perkin Trans. 1* **1983**, 2629.
[201] a) J. B. Jones, I. J. Jacovac, *J. Org. Chem.* **1979**, *44*, 2165; b) T. Mukaiyama, K. Fujimoto, T. Hirose, T. Takeda, *Chem. Lett.* **1980**, 635; c) T. Mukaiyama, K. Fujimoto, T. Takeda, *Chem. Lett.* **1979**, 1207; d) S. Takano, K. Ohashi, T. Sugihara, K. Ogasawara, *Chem. Lett.* **1991**, 203.

^{1}H-NMR (400 MHz, $CDCl_3$):

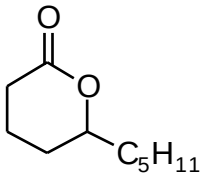
δ = 2.28 (dd, *J* = 17.4, 6.7 Hz, 1H), 2.60 (dd, *J* = 17.4, 7.7 Hz, 1H), 2.75-2.78 (m, 2H), 2.81-2.91 (m, 1H), 4.03 (dd, *J* = 9.0, 5.9 Hz, 1H), 4.33 (t, *J* = 9.1, 6.7 Hz, 1H), 7.13-7.17 (m, 2H), 7.21-7.35 (m, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$):

δ = 34.2, 37.2, 38.9, 72.7, 126.8, 128.7, 128.8, 134.6, 138.2, 176.8.

GC: Lipodex B (25 m × 0.25 mm) with pre-column (3 m × 0.25 mm); 60 kPa N_2; 170 °C isothermal; t_R = 59.1 and 64.1 min.

5.3.6 *rac*-6-Pentyl-tetrahydro-pyran-2-one (30)[51,202]



Starting from 2-*n*-pentylcyclobutanone (771 mg, 5 mmol), the product was synthesized according to the general procedure GP3.

774 mg; yield = 91%

^{1}H-NMR (400 MHz, $CDCl_3$):

δ = 0.89 (t, *J* = 6.8 Hz, 3H), 1.25-1.35 (m, 5H), 1.40-1.60 (m, 3H), 1.65-1.75 (m,1H) 1.83-1.97 (m,3H), 2.40-2.48 (m, 1H), 2.55-2.61 (m, 1H), 4.27-4.32 (m, 1H).

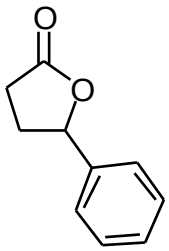
^{13}C-NMR (100 MHz, $CDCl_3$):

δ = 14.3, 18.8, 22.9, 24.9, 28.0, 29.7, 31.9, 36.0, 80.8, 172.2.

GC: Ultra-2 (25 m × 0.2 mm × 0.33 μm); 50 kPa N_2; 100 °C, 5 min, 30 °C/min, 250 °C, 5 min, 30 °C/min, 300 °C, 15 min; t_R = 11.8 min.

[202] B. Haase, M. P. Schneider, *Tetrahedron: Asymmetry* **1993**, *4*, 1017.

5.3.7 *rac*-3-(Phenyl)-dihydrofuran-2-one (*rac*-92)[203]



Starting from *rac*-2-phenylcyclobutanone (324 mg, 2 mmol), the product was synthesized according to the general procedure GP3.

316 mg; yield = 89%

^{1}H-NMR (400 MHz, $CDCl_3$):

δ = 2.12-2.25 (m, 1H) 2.61-2.70 (m, 3H), 5.51 (dd, *J* = 1.8, 8.1 Hz, 1H), 7.31-741 (m, 5H)

^{13}C-NMR (100 MHz, $CDCl_3$):

δ = 29.3, 31.3, 81.6, 125.5, 128.6, 129.0, 139.5, 177.2

GC: Ultra-2 (25 m × 0.2 mm × 0.33 μm); 50 kPa N_2; 100 °C, 5 min, 30 °C/min, 250 °C, 5 min, 30 °C/min, 300 °C, 15 min; t_R = 11.9 min.

Lipodex β-I/P (25 m × 0.25 mm) with pre-column (3 m × 0.25 mm); 100 kPa N_2; 140 °C isothermal with t_R = 102.2 and 106.2 min.

[203] a) A. L. Gutman, K. Zuobi, T. Bravdo, *J. Org. Chem.* **1990**, *55*, 3546; b) F. Ozawa, A. Kubo, T. Hayashi, *J. Am. Chem. Soc*. **1991**, *113*, 1417; c) Y.-C. Pai, J.-M. Fang, S.-H. Wu, , *J. Org. Chem.* **1994**, *59*, 6018.

5.4 Synthesis of the ligands

5.4.1 Synthesis of BINOL-derivatives

5.4.1.1 Resolution of *rac*-2,2′-dihydroxy-1,1′-dinaphthyl (*rac*-37)

The resolution was performed according to the standard procedure by Verhoeven and co-workers. [204]

Optical rotation: $[\alpha]_D$ = +33.0 (*c* = 0.975, THF) [(*R*)-BINOL]; −32.0 (*c* = 0.985, THF) [(*S*)-BINOL].

^{1}H-NMR (400 MHz, $CDCl_3$):

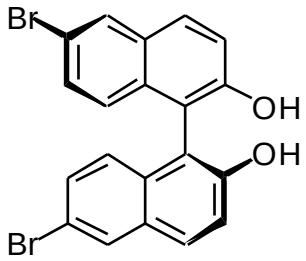
δ = 4.84 (br s, 2H), 7.12 (d, *J* = 8.3 Hz, 2H), 7.25-7.36 (m, 6H), 7.85 (d, *J* = 7.4 Hz, 2H), 7.91 (d, *J* = 8.8 Hz, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$):

δ = 110.80, 117.71, 124.00, 124.17, 127.44, 128.35, 129.38, 131.33, 133.37, 152.67.

HPLC: Daicel Chiralpak OP(+) (lenght 25 cm, diameter 0.46 cm), MeOH = 100 %, 0.5 mL/min, 25 °C, 254 nm; t = 15.2 min [(*R*)-BINOL], 26.0 min [(*S*)-BINOL].

5.4.1.2 (*S*)-6,6′-Dibromo-2,2′-dihydroxy-1,1′-dinaphthyl [(*S*)-97][205]



To a solution of 2.10 g of (*S*)-BINOL ((*S*)-**23**) (7.4 mmol) in 40 mL of dichloromethane at −80 °C was added dropwise 1 mL of bromine over a period of 30 minutes. After being stirred for an additional 2.5 h while warming to room temperature, the excess Br_2 was destroyed by addition of 50 mL of a 10% aqueous solution of $NaHSO_3$. The layers were separated and the

[204] D. Cai, D. L. Hughes, T. R. Verhoeven, P. J. Reider, *Tetraedron Lett.* **1995**, *36*, 7991.
[205] G. Dotsevi, Y. Sogah, D. J. Cram, *J. Am. Chem. Soc.* **1979**, *101*, 3035.

organic layer was washed with brine and dried over $MgSO_4$. Evaporation of the solvent under reduced pressure was followed by recrystallization.

3.02 g; yield = 92%

^{1}H-NMR (300 MHz, $CDCl_3$):

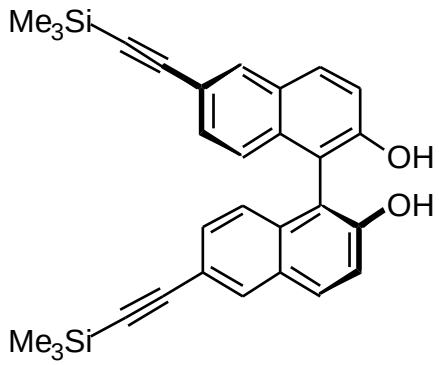
δ = 4.7 (br s, 2H), 6.93 (d, *J* = 8.7 Hz, 2H), 7.33 (d, *J* = 8.7 Hz, 2H), 7.33 (dd, *J* = 8.7, 2.0 Hz, 2H), 7.84 (d, *J* = 9.1 Hz, 2H), 8.01 (d, *J* = 2.0 Hz, 2H).

^{13}C-NMR (750 MHz, $CDCl_3$):

δ = 110.7, 118.0, 118.9, 125.9, 130.4, 130.5, 130.6, 130.8, 131.9, 152.9.

HPLC: Daicel Chiralpak OP(+) (length 25 cm, diameter 0.46 cm), MeOH = 100%, 0.5 mL/min, 25 °C, 254 nm; t = 21.2 min [(*S*)-**35**].

5.4.1.3 (*S*)-6,6′-Di(trimethylsilylacetylene)-2,2′-dihydroxy-1,1′-dinaphthyl [(*S*)-**99**][206]



To a mixture of 0.85 mL of trimethylsilylacetylene (6 mmol) and 1 g of (*S*)-6,6′-dibromo-2,2′-dihydroxy-1,1′-dinaphthyl (2.25 mmol) in triethylamine (20 mL) was added a catalytic amount of $PdCl_2$ (19.5 mg, 0.1 mmol), PPh_3 (115.3 mg, 0.4 mmol) and copper(I) iodide (11.4 mg, 0.06 mmol). The reaction mixture was stirred at 70 °C for 48 h under argon and then the solvent was removed under reduced pressure. Finally, the residue was diluted in ethylacetate and filtered through a silica plug. The crude product was subjected to colum chromatography to obtain the pure product.

[206] a) M. S. Wong, J.-F. Nicoud, *Chem. Commun.* **1994**, 249; b) K. Onitsuka, Y. Harada, F. Takei, S. Takahashi, *Chem. Commun.* **1998**, 643.

453 mg; yield = 42%

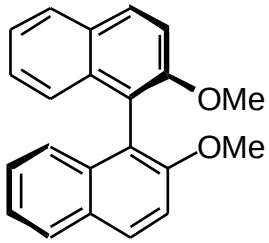
^{1}H-NMR (400 MHz, $CDCl_3$):

δ = 0.26 (s, 18H), 5.08 (s, 2H), 7.01 (d, *J* = 8.8 Hz, 2H), 7.32 (dd, *J* = 1.7, 8.8 Hz, 2H), 7.36-7.40 (m, 2H), 7.91 (d, *J* = 8.8 Hz, 2H), 8.04 (d, *J* = 1.8 Hz, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$):

δ = 94.4, 104.9, 110.5, 118.3, 118.6, 123.9, 128.1, 128.7, 130.1, 131.2, 132.2, 132.7, 153.2.

5.4.1.4 (*R*)-2,2′-Dimethoxy-1,1′-dinaphthyl [(*R*)-255][207]



To a stirred suspension of 12,51 g of (*R*)-2,2′-dihydroxy-1,1′-dinaphthyl (**37**) in acetone (400 mL) under argon were added 20 g of K_2CO_3 (15 mmol) and 30 g of CH_3I (0.21 mmol). The mixture was refluxed for 24 h. An additional portion of CH_3I (10 g, 0.07 mol) was added and the mixture was refluxed for further 12 h. Then, the solvent was partially evaporated and water was added to the suspension which was stirred for 8 h. Afterwards, the solid was collected, washed with water and with few mL of dichloromethane. It was dried in vacuo at 100 °C for 36 h to give the desired product as a white powder that was used without further purification in the next reaction.

12.57 g; yield = 93%

^{1}H-NMR (500 MHz, $CDCl_3$):

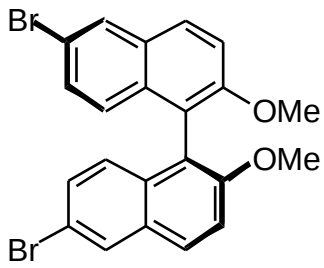
δ = 3.75 (s, 6H), 7.10 (d, *J* = 8.5 Hz, 2H), 7.18-7.23 (m, 2H), 7.30 (ddd, *J* = 7.5, 6.7, 1.2 Hz, 2H), 7.44 (d, *J* = 9.2 Hz, 2H), 7.85 (d, *J* = 8.2 Hz, 2H), 7.96 (d, *J* = 8.9 Hz, 2H).

^{13}C-NMR (125 MHz, $CDCl_3$):

δ = 56.9, 114.2, 119.5, 123.5, 125.2, 126.3, 127.9, 129.2, 129.4.

[207] D. S. Lingenfelter, R. G. Helgeson, D. J. Cram, *J. Org. Chem.* **1981**, *46*, 393.

5.4.1.5 (*S*)-6,6'-Dibromo-2,2′-dimethoxy-1,1′-dinaphthyl [(*S*)-256][194]



The methylation was performed according to the protocol under 1.4.1.4 for unsubstituted BINOL starting from (*S*)-6,6'-dibromo-BINOL (2.9 g, 6.5 mmol) in acetone (65 mL) with K_2CO_3 (3.3 g, 24 mmol) and CH_3I (1st addition = 4.9 g, 34.7 mmol; 2nd addition = 1,6 g, 11,7 mmol).

2.6 g; yield = 86%

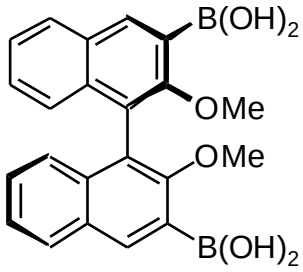
^{1}H-NMR (300 MHz, $CDCl_3$):

δ = 5.2 (s, 6H), 6.93 (d, *J* = 8.7 Hz, 2H), 7.33 (d, *J* = 8.7 Hz, 2H), 7.33 (dd, *J* = 8.7, 2.0 Hz, 2H), 7.84 (d, *J* = 9.1 Hz, 2H), 8.01 (d, *J* = 2.0 Hz, 2H).

^{13}C-NMR (750 MHz, $CDCl_3$):

δ = 110.7, 118.0, 118.9, 125.9, 130.4, 130.5, 130.6, 130.8, 131.9, 152.9.

5.4.1.6 (*R*)-3,3′-Bis(dihydroxyborane)-2,2′-dimethoxy-1,1′-dinaphthyl [(*R*)-257][208]



In a 500 mL flame-dried three-necked round-bottomed flask equipped with a N_2-inlet were placed Et_2O (200 mL) and TMEDA (4.58 g, 39 mmol). To this solution was added 1.6 M *n*-BuLi in hexane (25 mL, 40 mmol). The solution was stirred for 30 min at room temperature, solid (*R*)-**255** (4.16 g, 13.6 mmol) was added in one portion and the reaction mixture was stirred for 3 h. The resulting light brown suspension was cooled to -78 °C and $B(OEt)_3$ (12.4

[208] K. B. Simonsen, K. V. Gothelf, K. A. Jørgensen, *J. Org. Chem.* **1998**, *63*, 7536.

g, 84.5 mmol) was added via syringe over a period of 10 min. The solution was allowed to warm to room temperature and was left stirring overnight. Afterwards, the reaction mixture was cooled to 0 °C, 1 M HCl (100 mL) was added and it was stirred for 2 h. For work up, the phases were separated and the organic phase was washed twice with 1 M aqueous HCl (80 mL) and brine (100 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure and the resulting white solid was recrystallized from toluene to give (*R*)-**257**.

4.65 g; yield = 85%

^{1}H-NMR (300 MHz, $CDCl_3$):

δ = 3.41 (s, 6H), 7.11 (dd, *J* = 8.1, 1.1 Hz, 2H), 7.34 (td, *J* = 7.5, 1.2 Hz, 2H), 7.46 (td, *J* = 7.4, 1.2 Hz, 2H), 8.05 (d br, *J* = 7.1 Hz, 2H), 8.56 (s, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$):

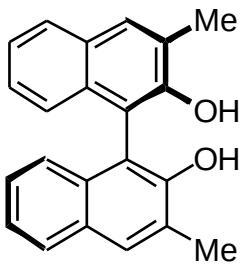
δ = 61.8, 124.2, 125.7, 126.3, 128.2, 129.7, 131.4, 136.6, 139.1, 161.2.

5.4.2 General protocol for the Suzuki cross-coupling reaction (GP4).[208]

a) In a 50 mL two-necked flask equipped with a condenser were placed (*R*)-BINOL boronic acid **257** (0.75 g, 1.9 mmol), $Ba(OH)_2 \cdot 8H_2O$ (1.74 g, 5.5 mmol), and $Pd(PPh_3)_4$ (0.116 g, 0.1 mmol), and the flask was evacuated and filled with N_2 three times. 1,4-Dioxane (12 mL), H_2O (4 mL), and the appropriate bromoarene or iodoalkane (6.0 mmol) were added. The reaction mixture was then refluxed for 24 h under N_2 and cooled to room temperature. The dioxane was removed and the resulting phase was redissolved in CH_2Cl_2 (75 mL), washed with 1 M aqueous HCl (2 x 50 mL) and brine (75 mL) and dried over Na_2SO_4. The solvent was removed under reduced pressure to give the crude product as a yellow semicrystalline oil.

b) The crude product was dissolved in dry CH_2Cl_2 (75 mL) and cooled to 0 °C, BBr_3 (1 mL) was added over a period of 10 min and the reaction mixture was stirred for 18 h at room temperature. The pale yellow solution was cooled to 0 °C and H_2O (150 mL) was carefully added. The phases were separated and the organic phase was washed with water (2 x 100 mL) and brine (100 mL), dried over Na_2SO_4, and concentrated under reduced pressure. The resulting solid was subjected to purification by column chromatography on silica to give the desired product.

5.4.2.1 (*R*)-3,3′-Bis(methyl)-2,2′-dihydroxy-1,1′-dinaphthyl [(*R*)-93][209]



Starting from iodomethane (851 mg, 6 mmol) the product was synthesized according to the general protocol GP4.

382 mg; yield = 64%

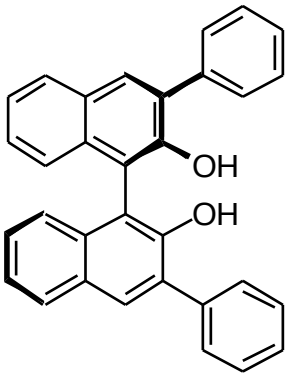
^{1}H-NMR (400 MHz, $CDCl_3$):

δ = 2.5 (s, 6H), 5.11 (s, 2H), 7.07 (d, *J* = 9.6 Hz, 2H), 7.20-7.25 (m, 2H), 7.30-7.35 (m, 2H), 7.79-7.81 (m, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$):

δ = 17.4, 110.7, 124.1, 124.3, 126.6, 127.2, 127.8, 129.6, 130.9, 132.4, 152.3.

5.4.2.2 (*R*)-3,3′-Bis(phenyl)-2,2′-dihydroxy-1,1′-dinaphthyl [(*R*)-69][208]



Starting from bromobenzene (942 mg, 6 mmol) the product was synthesized according to the general protocol GP4. The crude product was purified by column chromatography (silica, hexane:EtOAc = 19:1).

608 mg; yield = 73%

[209] D. J. Cram, R. C. Helgelson, S. C. Peacock, L. J. Kaplan, L. A. Domeier, P. Moreau, K. Koga, J. M. Mayer, Y. Chao, *J. Org. Chem.* **1978**, *43*, 1930.

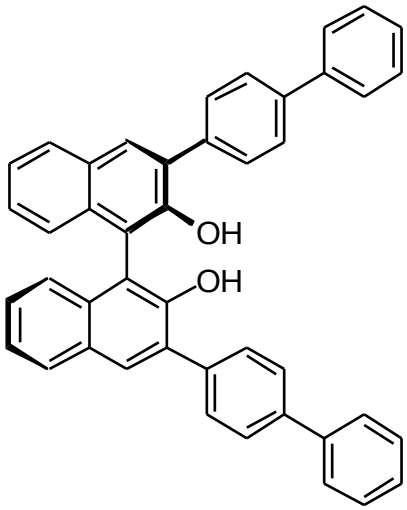
^{1}H-NMR (300 MHz, $CDCl_3$):

δ = 5.36 (s, 2H), 7.25-7.52 (m, 12 H), 7.45 (m, 4H), 7.93 (d, *J* = 7.7 Hz, 2H), 8.03 (s, 2H).

^{13}C-NMR (75 MHz, $CDCl_3$):

δ = 112.4, 124.3, 124.4, 127.4, 127.8, 128.5, 128.5, 129.5, 129.6, 130.7, 131.4, 133.0, 137.5, 150.2.

5.4.2.3 (*R*)-3,3′-Bis(diphenyl)-2,2′-dihydroxy-1,1′-dinaphthyl [(*R*)-94][208]



Starting from 4-bromobiphenyl (1.39 g, 6 mmol) the product was synthesized according to the general protocol GP4.

739 mg; yield = 66%

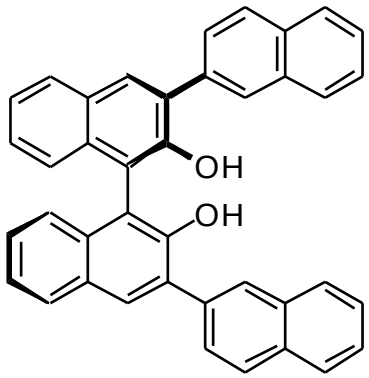
^{1}H-NMR (400 MHz, $CDCl_3$):

δ = 5.39 (s, 2H), 7.23-7.46 (m, 12H), 7.64 (d, *J* = 7.2 Hz, 4H), 7.70 (d, *J* = 8.3 Hz, 4H), 7.81 (d, *J* = 8.3 Hz, 4H), 7.91 (d, *J* = 7.7 Hz, 2H), 8.06 (s, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$):

δ = 112.3, 124.2, 124.4, 127.1, 127.2, 127.4, 128.5, 128.8, 129.5, 130.0, 130.2, 131.4, 132.9, 136.4, 140.5, 140.7, 150.2.

5.4.2.4 (*R*)-3,3′-Bis(2-naphthyl)-2,2′-dihydroxy-1,1′-dinaphthyl [(*R*)-95][208]



Starting from 2-bromonaphthalene (1.24 g, 6 mmol) the product was synthesized according to the general protocol GP4. The crude product was purified by column chromatography (silica, CH_2Cl_2:hexane 1:1).

716 mg; yield 70%

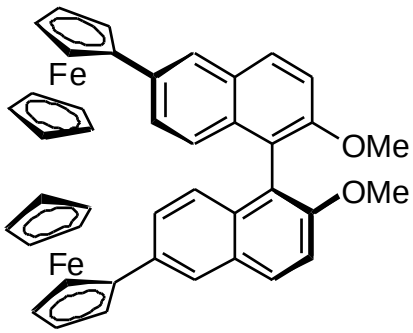
^{1}H-NMR (400 MHz, $CDCl_3$):

δ = 5.50 (s, 2H), 7.31-7.62 (m, 10 H), 7.88-7.97 (m, 10 H), 8.16 (s, 2H), 8.24 (s, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$):

δ = 112.5, 124.4, 124.4, 126.3, 126.3, 127.5, 127.7, 128.0, 128.2, 128.5, 129.6, 130.7, 131.7, 132.8, 133.1, 133.5, 135.0, 150.3.

5.4.2.5 (*S*)-6,6′-Bis(ferrocene)-2,2′-methoxy-1,1′-dinaphthyl [(*R*)-258]



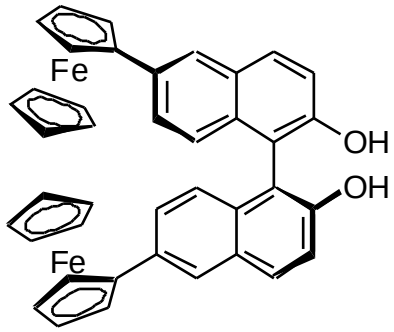
Starting from (*S*)-6,6'-dibromo-2,2'-dimethoxy-1,1'-binaphthyl (1 g, 2.1 mmol) and ferrocenyl boronic acid (1 g, 4.2 mmol) the product was synthesized according to the general protocol GP4a.

275 mg; yield = 20%

^{1}H-NMR (300 MHz, $CDCl_3$):

δ = 3.80 (s, 6H), 4.04 (s, 10H), 4.32 (br, 4H), 4.71 (d, *J* = 4.7 Hz, 4H), 7.09 (d, *J* = 8.8 Hz, 2H), 7.40 (dd, *J* = 8.6, 1.7 Hz, 2H), 7.45 (d, *J* = 9.0 Hz ,2H), 7.88 (d, *J* = 1.4 Hz, 2H), 7.93 (d, *J* = 8.8 Hz, 2H).

5.4.2.6 (*S*)-6,6′-Bis(ferrocene)-2,2′-hydroxy-1,1′-dinaphthyl [(*R*)-98]



Starting from (*S*)-6,6'-bisferrocenyl-2,2'-dimethoxy-1,1'-binaphthyl (**258**) (275 mg, 0.2 mmol) the product was synthesized according to the general protocol GP4b.

105 mg; yield = 79%

^{1}H-NMR (300 MHz, $CDCl_3$):

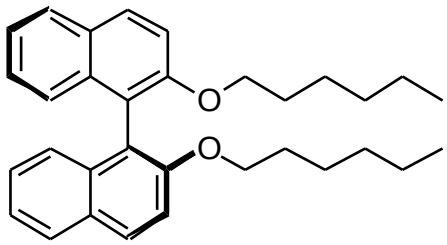
δ = 4.06 (s, 10H), 4.36 (br, 4H), 4.71 (d, *J* = 5.3 Hz, 4H), 5.05 (s, 2H), 7.16 (d, *J* = 9.8 Hz, 2H), 7.40 (d, *J* = 8.8 Hz, 2H), 7.50 (dd, *J* = 8.7, 1.3 Hz, 2H), 7.91 (br, 2H), 7.94 (d, *J* = 9.1 Hz, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$):

δ = 66.8, 66.9, 69.4, 69.8, 118.2, 124.4, 124.5, 127.2, 129.9, 131.2, 132.1, 152.4, 158.1.

5.4.3 Synthesis of (*S*)-4,4′,6,6′-Tetrabromo-2,2′-hydroxy-1,1′-binaphthyl

5.4.3.1 (*S*)-2,2′-Hexyloxy-1,1′-binaphthyl [(*S*)-259][75]



To a solution of (*S*)-BINOL (3.0 g, 10.5 mmol) and 1-bromohexane (6 mL, 52.5 mmol) in acetonitrile (50 mL) was added K_2CO_3 (7.5 g, 52.5 mmol). The resulting mixture was degassed with nitrogen and then refluxed for 16 h. After the mixture was cooled to room temperature again, water was added, the mixture was extracted with hexane and the organic layer was washed with brine. Eventually evaporation of the solvent followed by flash chromatography on silica gel with hexane as eluent afforded (*S*)-**259** as a colourless oil.

4.5 g; yield = 95%

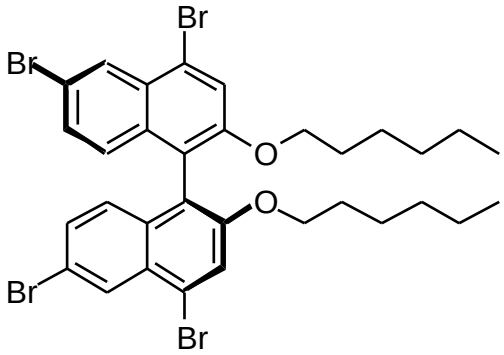
^{1}H-NMR (400 MHz, $CDCl_3$):

δ = 0.77-0.72 (m, 6H), 1.07-0.91 (m, 12H), 1.44-1.37 (m, 4H), 3.98-3.89 (m, 4H), 7.33-7.17 (m, 6 H), 7.41 (d, *J* = 9.0 Hz, 2H), 7.84 (d, *J* = 8.1 Hz, 2H), 7.92 (d, *J* = 9.0 Hz, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$):

δ = 13.9, 22.4, 25.2, 29.3, 31.3, 69.8, 115.9, 120.7, 123.3, 125.5, 125.9, 127.7, 128.9, 129.3, 134.2, 154.5.

5.4.3.2 (*S*)-4,4′,6,6′-Tetrabromo-2,2′-hexyloxy-1,1′-binaphthyl [(*S*)-260][75]



To a solution of (*S*)-**259** (4.5 g, 10 mmol) in glacial acetic acid (100 mL) was added Br_2 (5.2

mL, 100 mmol) over 30 min at room temperature. The reaction mixture was stirred for 6 h and then, a saturated aqueous solution of $NaHSO_3$ was added to destroy excessive Br_2. After being extracted with ethyl acetate, the combined organic solution was washed with brine. The residue was finally purified by column chromatography on silica gel with hexane as the eluent to give the product as a slightly yellow oil.

6.0 g; yield = 78%

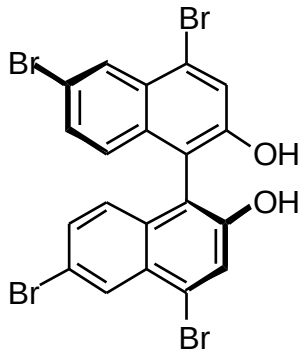
^{1}H-NMR (400 MHz, $CDCl_3$):

δ = 0.72-1.08 (m, 18H) 1.38-1.43 (m, 4H), 3.89-3.96 (m, 4H), 6.97 (d, *J* = 9.0 Hz, 2H), 7.30 (dd, *J* = 2.1, 9.0 Hz, 2H), 7.70 (s, 2H), 8.39 (d, *J* = 2.1 Hz, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$):

δ = 14.04, 22.6, 25.5, 29.3, 31.4, 69.9, 119.4, 119.5, 120.5, 122.5, 127.5, 129.0, 129.5, 130.7, 133.3, 154.6.

5.4.3.3 (*S*)-4,4′,6,6′-Tetrabromo-2,2′-hydroxy-1,1′-binaphthyl [(*S*)-104][75]



Starting from (*S*)-4,4′,6,6′-Tetrabromo-2,2′-hexyloxy-1,1′-binaphthyl (1.5 g, 1.96 mmol) the product was synthesized according to the general protocol GP4b.

955 mg; yield = 81%

^{1}H-NMR (400 MHz, $CDCl_3$):

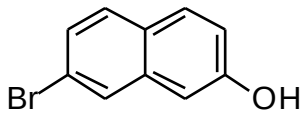
δ = 5.45 (s, 2H), 6.97 (d, *J* = 9.0 Hz, 2H), 7.30 (dd, *J* = 2.1, 9.0 Hz, 2H), 7.70 (s, 2H), 8.39 (d, *J* = 2.1 Hz, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$):

δ = 111.1, 119.9, 123.3, 124.8, 126.5, 129.5, 130.2, 131.9, 132.7, 152.7.

5.4.4 Synthesis of (*R*)-(2)-7,7′-Dibromo-2,2′-dihydroxy-1,1′-binaphthyl

5.4.4.1 7-Bromo-2-hydroxynaphthalene (101)[73]



To a stirred suspension of triphenylphosphane (18.3 g, 68.75 mmol) in CH_3CN (150 mL) cooled to 0°C, bromine (3.52 mL, 68.75 mmol) was slowly added over 30 min. After the addition, the mixture was warmed to room temperature and 2-hydroxynaphthalene (11.01 g, 68.74 mmol) was added as one portion. The resulting mixture was heated at 80 °C for 2 h, then the solvent was removed by distillation under reduced pressure. The dark residue obtained was heated at 250 °C for 6 h. Afterwards, the mixture was cooled to room temperature and then purified by chromatography on silica gel to give **101** as a pale yellow solid.

4.4 g; yield = 29%

^{1}H-NMR (400 MHz, $CDCl_3$):

δ = 5.15 (br s, 1 H), 7.06 (d, *J* = 2.5 Hz, 1H), 7.11 (dd, *J* = 2.5, 8.8 Hz, 1H), 7.40 (dd, *J* = 2.0, 8.7 Hz, 1H), 7.63 (d, *J* = 8.7 Hz, 1H), 7.73 (d, *J* = 8.8 Hz, 1H), 7.84 (d, *J* = 2.0 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$):

δ = 109.7, 119.2, 121.9, 128.1, 128.4, 129.4, 130.4, 130.9, 136.8, 155.2.

5.4.4.2 (±)-7,7′-Dibromo-2,2′-dihydroxy-1,1′-binaphthyl (102)[73]

To a solution of **101** (4.4 g, 19.7 mmol) and $CuCl_2$ (5.3 g, 40 mmol) in degassed methanol (100 mL) under N_2 was added a solution of *tert*-butylamine (17 mL, 161 mmol) in methanol (67 mL) over a period of 2 h. After the resulting solution had been stirred at room temperature for 24 h, the solution was cooled to 0°C, then a 6 N aqueous solution of HCl was carefully added. The methanol was evaporated under reduced pressure and the residue was diluted with ethyl acetate (200 mL) and washed with brine (2 x 100 mL). The organic phase was separated, dried and concentrated under reduced pressure to give a residue which was then purified by flash chromatography (cyclohexane:ethyl ether = 1:4). The solid was further purified by recrystallization from cyclohexane.

3.2 g; yield = 74%

^{1}H-NMR (400 MHz, $CDCl_3$):

δ = 5.12 (br s, 2 H), 7,24 (d, *J* = 1.6 Hz, 2H), 7.39 (d, *J* = 8.8 Hz, 2H), 7.48 (dd, *J* = 1.6, 8.6 Hz, 2H), 7.78 (d, *J* = 8.6 Hz, 2H), 7.96 (d, *J* = 8.8 Hz, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$):

δ = 110.1, 118.8, 122.9, 126.4, 128.2, 128.4, 130.6, 132.1, 135.1, 154.1.

5.4.4.3 Resolution of (±)-7,7′-dibromo-2,2′-dihydroxy-1,1′-binaphthyl (102)[73]

To a stirred solution of (±)-**102** (3.2 g, 7.2 mmol) and (1*R*,2*S*,5*R*)-menthylchloroformate (3.25 mL, 15 mmol) in THF (30 mL), a solution of Et_3N (4.4 mL, 31.7 mmol) in THF (15 mL) was added under nitrogen. The resulting homogeneous solution was stirred at room temperature for 4 h, then the solvent was evaporated under reduced pressure and the residue was dissolved in $CHCl_3$ (25 mL). The solution was washed with a aqueous solution of 2 N HCl (5 mL) and brine, then the organic phase was separated, dried and concentrated under reduced pressure to give a solid. The solid was recrystallized three times from hexane affording the diastereomerically pure compound **103**.

2.6 g ;Yield = 45%

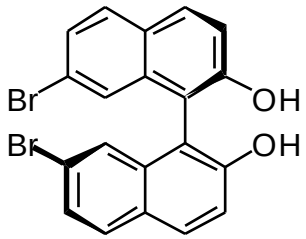
^{1}H-NMR (400 MHz, $CDCl_3$):

δ = 0.1 (d, *J* = 6.8 Hz, 6H), 0.25 (d, *J* = 7.1 Hz, 6H), 0.38-0.60 (m, 14H), 0.75-0.89 (m, 4H), 0.93- 1.05 (m, 2H), 1.18-1.30 (m, 4H), 1.51-1.97 (m, 2H), 3.96 (m, 2 H), 7.35 (d, *J* = 2.0 Hz, 2H), 7.52 (d, *J* = 8.9 Hz, 2H), 7.56 (dd, *J* = 2.0, 8.7 Hz, 2H), 7.81 (d, *J* = 8.9 Hz, 2H), 7.98 (d, *J* = 8.7 Hz, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$):

δ = 17.1, 21.3, 22.9, 24.4, 27.1, 32.3, 34.9, 41.3, 47.6, 80.3, 122.7, 123.1, 123.2, 129.0, 130.6, 130.8, 131.1, 131.2, 135.2, 148.8, 153.5.

5.4.4.4 (*R*)-(2)-7,7′-Dibromo-2,2′-dihydroxy-1,1′-binaphthyl [(*R*)-102][73]



To a solution of diastereopure **103** (2.2 g, 2.8 mmol) in THF (50 mL) was added $LiAlH_4$ (1.5 g, 40 mmol), in portions over 1 h. After 2 h of stirring, the reaction was quenched by adding an aqueous solution of 3 N HCl (80 mL). After the evaporation of THF under reduced pressure, the mixture was extracted with CH_2Cl_2 (3 x 50 mL) and the organic phases were collected, dried and concentrated under reduced pressure to give a solid which was purified by flash chromatography (eluant cyclohexane/ethyl ether, 9:1). The solid was further purified by recrystallization from cyclohexane.

932 mg; yield = 75%

^{1}H-NMR (400 MHz, $CDCl_3$):

δ = 5.12 (br s, 2 H), 7,24 (d, *J* = 1.6 Hz, 2H), 7.39 (d, *J* = 8.8 Hz, 2H), 7.48 (dd, *J* = 1.6, 8.6 Hz, 2H), 7.78 (d, *J* = 8.6 Hz, 2H), 7.96 (d, *J* = 8.8 Hz, 2H).

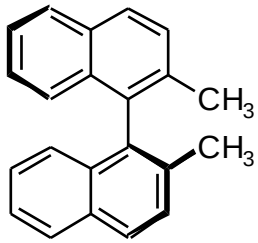
^{13}C-NMR (100 MHz, $CDCl_3$):

δ = 110.1, 118.8, 122.9, 126.4, 128.2, 128.4, 130.6, 132.1, 135.1, 154.1.

HPLC: *ee* = 99%; Chiralcel OD-H column (eluant *n*-hexane/*i*PrOH (92:8), flow rate of 0.5 mL/min, UV detection).

5.4.5 (*S*)-4,4-dibromo-4,5-dihydro-3*H*-dinaphtho[2,1-c:1′,2′-e]stannepin

5.4.5.1 (*S*)-2,2′- Dimethyl-1,1′-binaphthyl [(*S*)-178][210]



To a solution of (*S*)-bistriflate BINOL (3 g, 5.5 mmol) and $NiCl_2$(dppb) (148 mg, 0.3 mmol) in diethyl ether (40 mL) was added dropwise methylmagnesium bromide (3 M, 1.1 mL) at 0 °C. The reaction mixture was heated to reflux for 24 h. Thereafter, the reaction was quenched by slow addition of water (10 mL) at 0 °C and then diluted with 5% aqueous solution of HCl (10 mL). The aqueous layer was extracted with diethyl ether (3 x 10 mL) and the combined organic layers were washed with a saturated aqueous solution of $NaHCO_3$ (20 mL), dried over anhydrous sodium sulfate and concentrated to give the desired product as a light yellow solid.

1.5 g; yield = 99%

^{1}H-NMR (400 MHz, $CDCl_3$):

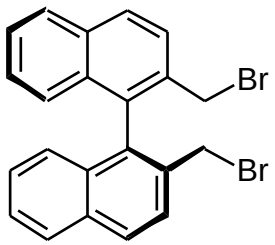
δ = 1.93 (s, 6H), 6.95-6.96 (m, 2H), 7.07-7.09 (m, 2H), 7.26-7.28 (m, 2H), 7.39-7.41 (m, 2H), 7.70-7.90 (m, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$):

δ = 20.5, 125.1, 125.9, 126.3, 127.7, 128.1, 128.9, 132.4, 133.0, 134.5, 135.4.

[210] S. Sengupta, M. Leite, D. S. Raslan, C. Quesnelle, V. Snieckus, *J. Org. Chem.* **1992**, *57*, 4066.

5.4.5.2 (*S*)-2,2′- dibromomethyl-1,1′-binaphthyl [(*S*)-179][139a]



To a solution of (*S*)-2,2′-dimethyl-1,1′-binaphthyl (0.43 g, 1.5 mmol) in carbontetrachloride (10 mL) were added 573 mg of *N*-bromosuccinimide (3.2 mmol) and a catalytic amount of AIBN. The mixture was heated at reflux and irradiated with a lamp for three days. The mixture was then cooled to room temperature and filtered. The filtrate was concentrated and passed through a silica gel plug. After removal of the solvent under reduced pressure the residue was recrystallized from CH_2Cl_2/pentane to afford the pure product

580 mg; yield = 87%

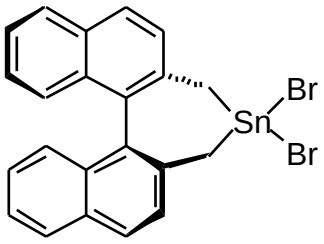
^{1}H-NMR (400 MHz, $CDCl_3$):

δ = 4.26 (s, 4H), 7.07 (d, *J* = 7.9 Hz, 2H), 7.25-7.29 (m, 2H), 7.47-7.51 (m, 2H), 7.75 (d, *J* = 8.5 Hz, 2H), 7.92-7.94 (d, *J* = 7.7 Hz, 2H), 8.01-8.03 (d, *J* = 8.5 Hz, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$):

δ = 33.0, 127.0, 127.1, 127.9, 128.2, 129.5, 133.0, 133.4, 134.4, 134.9.

5.4.5.3 (*S*)-4,4-dibromo-4,5-dihydro-3*H*-dinaphtho[2,1-c:1′,2′-e]stannepin [(S)-176][139]



To a solution of (*S*)-2,2′-dibromomethyl-1,1′-binaphthyl (290 mg, 0.65 mmol) in 9 mL of toluene containing 4 µl of water were added 171 mg of tin powder (1.44 mmol) and the mixture was heated to reflux under a nitrogen atmosphere for 5 h. After cooling, the tin powder was filtered and washed with toluene, the organic solutions were combined and the

solvent was evaporated under reduced pressure. The solid residue was suspended in diethyl ether, stirred for few minutes and filtered to give the desired complex.

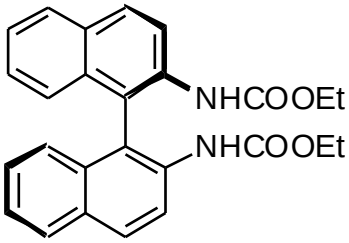
100 mg; yield = 28%

^{1}H-NMR (400 MHz, $CDCl_3$):

δ = 2.98 (d, *J* = 11.3 Hz, ^2J ($^{117/119}$Sn,^{1}H) = 76.5 Hz, 2H), 3.29 (d, *J* = 11.3 Hz, ^2J ($^{117/119}$Sn,^{1}H) = 76.5, 2H), 7.01 (d, *J* = 8.4 Hz, 2H), 7.20-7.30 (m, 2H), 7.42-7.46 (m, 2H), 7.54 (d, *J* = 8.5 Hz, 2H), 7.91-7.95 (m, 4H).

5.4.6 Synthesis of *(S)*-*N*,*N*-dimethyl-*N*,*N*-bis(2-pyridylmethyl)-1,1′-binaphthyl

5.4.6.1 (*R*)-2,2′-Bis(ethoxycarbonylamino)-1,1′-binaphthyl [(*R*)-261][211]



To a stirred solution of enantiopure 2,2′-bisamino-1,1′-binaphthyl [(*R*)-BINAM] (1 g, 3.5 mmol) in benzene (20 mL) and pyridine (3 mL) was added dropwise a solution of ethyl chloroformate (0.94 g, 8.6 mmol) in benzene (5 mL). After the addition was complete, the mixture was stirred for 2 h at room temperature. The reaction was quenched by adding 25 mL of a 10% aqueous solution of NaOH. The resulting organic layer and the benzene extracts from the aqueous layer were combined, washed with water and dried over $MgSO_4$. The solvents were evaporated under reduced pressure and the resulting residue was recrystallized from ethanol-acetone to give the desired product.

899 mg; yield = 60%

[211] S. Miyano, M. Nawa, A. Mori, H. Hashimoto, *Bull. Chem. Soc. Jpn.* **1984**, *57*, 2171.

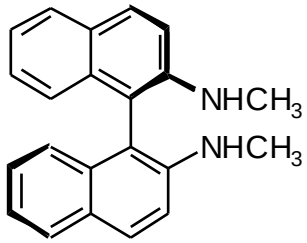
^{1}H-NMR (400 MHz, $CDCl_3$):

δ = 1.16 (t, *J* = 7.0 Hz, 6H), 4.05-4.11 (m, 4H), 6.27 (s, 2H), 6.97 (d, *J* = 8.5 Hz, 2H), 7.23-7.27 (m, 2H), 7.39-7.43 (m, 2H), 7.92 (d, *J* = 8.2 Hz, 2H), 8.06 (d, *J* = 9.1 Hz, 2H), 8.56 (d, *J* = 9.2 Hz, 2H).

^{13}C-NMR (750 MHz, $CDCl_3$):

δ = 14.3, 61.4, 117.3, 119.4, 124.7, 125.0, 127.3, 128.3, 130.2, 130.6, 132.5, 135.3, 153.6

5.4.6.2 (*R*)-2,2′-Bis(methylamino)1,1′-binaphthyl [(*R*)-201][211]



To a stirred suspension LAH (0.59 g, 15 mmol) in THF (15 mL) was added dropwise a solution of 2,2′-bis(ethoxycarbonylamino)-1,1′-binaphthyl ((*R*)-**261**) (899 mg, 2.11 mmol) in THF (5 mL) and the mixture was heated to reflux for 3 h. The reaction mixture was cooled in an ice-bath and the remaining hydride was carefully quenched by addition of water and then a 15% aqueous solution of NaOH. A white precipitate was filtered off and washed with diethyl ether. The combined filtrate and ether washings were washed with water and dried over Na_2SO_4 overnight. After the solvent was evaporated under reduced pressure, the residue was recrystallized from ethanol-benzene.

531 mg; yield = 83%

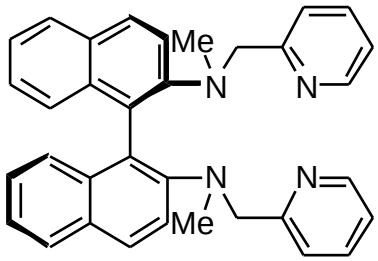
^{1}H-NMR (400 MHz, $CDCl_3$):

δ = 2.80 (d, *J* = 5.2 Hz, 6H), 4.06 (d, *J* = 5.0 Hz, 2H), 6.83 (d, *J* = 8.5 Hz, 2H), 7.06-7.14 (m, 4H), 7.27 (d, *J* = 8.9 Hz, 2H), 7.78-7.80 (m, 2H), 7.91 (d, *J* = 8.8, 2H).

^{13}C-NMR (750 MHz, $CDCl_3$):

δ = 30.7, 112.0, 114.1, 121.9, 124.1, 126.8, 128.2, 128.8, 130.1, 134.6, 146.5.

5.4.6.3 *(R)*-*N*,*N*-dimethyl-*N*,*N*-bis(2-pyridylmethyl)-1,1′-binaphthyl [(*R*)-202]



To a stirred solution of (*R*)-2,2′-bis(methylamino)1,1′-binaphthyl (**201**) (260 mg, 0.83 mmol) in CH_2Cl_2 (10 mL) was added the isolated free base 2-picolyl chloride (0.3 g, 2.4 mmol) (2-picolyl chloride·HCl was treated with aqueous K_2CO_3 and extracted with CH_2Cl_2), followed by addition of 1 M aqueous NaOH (2 mL). After 60 h of stirring at room temperature, the reaction mixture was diluted with 1 M aqueous NaOH. The aqueous layer was extracted with CH_2Cl_2 and the organic extracts were combined, dried over Na_2SO_4 and concentrated under reduced pressure.

328 mg, yield = 80 %

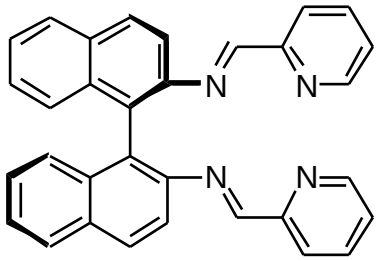
^{1}H-NMR (400 MHz, $CDCl_3$):

δ = 2.76 (s, 6H), 4.62 (s, 4H), 6.94-6.98 (m, 2H), 7.09-7.18 (m, 6H), 7.22 (d, *J* = 9.0 Hz, 2H), 7.40 (d, *J* = 7.7 Hz, 2H), 7.63 (td, *J* = 7.7, 1.7 Hz, 2H), 7.76 (d, *J* = 7.7 Hz, 2H), 7.87 (d, *J* = 8.8 Hz, 2H), 8.52 (d, *J* = 5.0 Hz, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$):

δ = 31.4, 47.1, 111.9, 113.7, 121.9, 123.0, 123.3, 123.9, 126.9, 127.8, 128.4, 129.9, 133.9, 137.3, 145.8, 149.6, 156.7.

5.4.7 *(R)*-*N*,*N*-Bis-pyridin-2-ylmethylene-1,1'binaphthalenyl-2,2'-diamine [*(R)*-200][212]



To a stirred solution of (*R*)-1,1'binaphthyl-2,2'-diamine (**194**) (284 mg, 1 mmol) in 10 mL of dry EtOH was added of picolinaldehyde (229 mg, 2.2 mmol) and the solution was heated to reflux for 2h. After being cooled to RT, the solvent was evaporated under reduced pressure and the solid was recrystallized from ethanol.

370 mg; yield = 80%

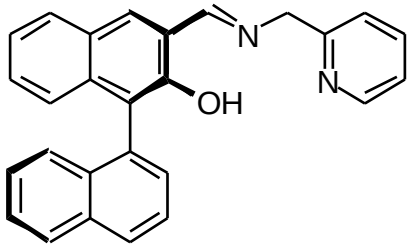
^{1}H-NMR (400 MHz, $CDCl_3$):

δ = 6.98-7.02 (m, 4H), 7.11-7.16 (m, 2H), 7.2-7.36 (m, 8H), 7.76-7.79 (d, *J* = 8 Hz, 2H), 7.85-7.88 (d, *J* = 8.8 Hz, 2H), 8.35 (d, *J* = 4.7 Hz, 2H), 8.38 (s, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$):

δ =115.5, 118.5, 121.4, 125.1, 125.4, 126.4, 128.2, 128.4, 129.8, 132.2, 133.6, 136.7, 147.4, 149.2, 154.8, 160.5

5.4.8 (*R*)-3-[(Pyridin-2-ylmethylimino-methyl]-1,1'-binaphthalenyl-2-ol [(*R*)-199][213]



[212] Z. Guo-Fu, C.-L. Yin, *J. Mol. Cat. A: Chemical* **1998,** 132.
[213] Z. Cimerman, S. Miljanic, N. Galic, *Croatica Chemica Acta* **2000**, *73*, 81.

To a stirring solution of (*R*)-2-hydroxy-[1,1']binaphthalenyl-3-carbaldehyde (200 mg, 0.67 mmol) in ethanol (8 mL), 2-picolylamine (73.6 mg, 0.7 mmol) was added and the solution was allowed to stir overnight. Then the solvent was evaporated and the solid was recrystallized from ethanol.

205 mg; yield = 75%

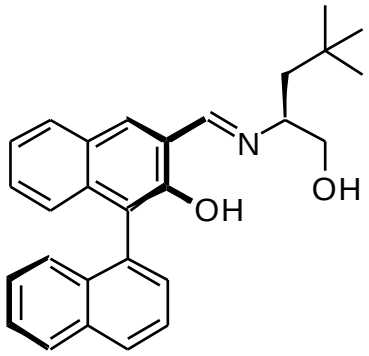
^{1}H-NMR (400 MHz, $CDCl_3$):

δ = 4.90 (s, 2H), 7.09-7.13 (m, 2H), 7.19-7.37 (m, 8H), 7.58 (t, *J* = 1.6, 7.6 Hz, 1H), 7.83-7.95 (m, 3H), 8.31 (d, *J* = 4.2Hz, 1H), 8.71 (s, 1H), 13.3 (br s, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$):

δ = 114.6, 118.3, 120.2, 121.1, 122.4, 122.7, 123.4, 124.1, 124.9, 125.1, 126.7, 127.9, 128.4, 129.2, 129.3, 129.4, 130.2, 133.9, 134.8, 135.7, 137.2, 166.7.

5.4.9 (*R*)-3-[(1-Hydroxymethyl-3,3-dimethyl-butylimino)-methyl]-[1,1']binaphthalenyl-2-ol [(*R*)-197][214]



To a stirring solution of (*R*)-2-hydroxy-[1,1']binaphthalenyl-3-carbaldehyde (200 mg, 0.67 mmol) in ethanol (8 mL), *tert*-leucinol (78.5 mg, 0.67 mmol) was added and the solution was allowed to stir overnight. Then, the solvent was evaporated under reduced pressure and the solid was recrystallized from ethanol.

234 mg; yield = 85%

^{1}H-NMR (400 MHz, $CDCl_3$):

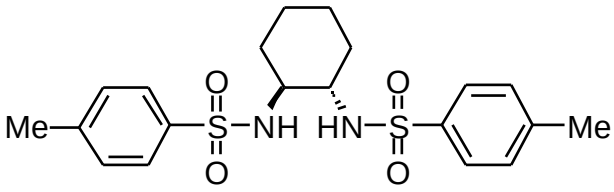
δ = 0.96 (s, 9H), 1.18-1.34 (m, 2H), 3.04 (dd, *J* = 2.5, 9.4 Hz, 1H), 3.93 (dd, *J* = 11.6, 2.3 Hz, 1H), 6.38 (t, *J* = 9.6 Hz, 1H), 7.10-7.40 (m, 8H), 7.85-7.95 (m, 3H), 8.06 (s, 1H), 8.63 (s, 1H).

[214] A. H. Vetter, A. Berkessel, *Tetrahedron Lett.* **1998**, *39*, 1741.

^{13}C-NMR (100 MHz, $CDCl_3$):

δ = 27.4, 33.7, 62.6, 82.0, 118.0, 121.0, 123.6, 124.3, 124.9, 126.7, 127.9, 128.5, 129.2, 129.3, 129.5, 130.3, 133.7, 134.9, 151.7, 165.9.

5.4.10 (1*R*,2*R*)-(–)-cyclohexane-(*p*-methyl)sulfonamide [(1*R*,2*R*)-163][120]



To a solution of (1*R*,2*R*)-(–)-diaminocyclohexane (500 mg, 4.38 mmol) and triethylamine (1.5 mL, 11 mmol) in dichloromethane (20 mL) at 0 °C was added of *p*-toluenesulfonylchloride (1.67 g, 8.76 mmol). The mixture was stirred for 10 minutes at 0 °C, then warmed to room temperature and stirred for additional 4 h. The solvent was evaporated under reduced pressure and the remaining white solid was purified by chromatography (silica gel, CH_2Cl_2:EtAc = 93:7). The chromatographed bissulfonamide was recrystallized from chloroform-hexane.

1.5 g; yield = 80%

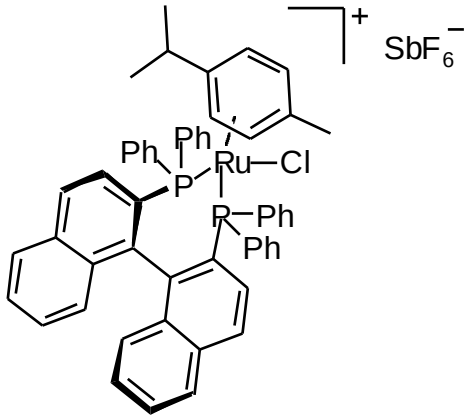
^{1}H-NMR (400 MHz, $CDCl_3$):

δ = 1.08-1.12 (m, 4H), 1.55-1.57 (m, 2H), 1.85-1.88 (m, 2H), 2.44 (s, 6H), 7.73-7.75 (m, 2H), 4.75 (d, *J* = 6 Hz, 2H), 7.31-7.33 (m, 4H), 7.74-7.77 (m, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$):

δ = 21.9, 24.6, 33.9, 56.9, 127.5, 129.9, 143.8.

5.5 {CymeneRu[(*S*)-tolyl-BINAP]}SbF_6 (182)[143]



A Schlenk tube was charged with $(CymeneRuCl_2)_2$ (72 mg, 0.12 mmol) and (*S*)-tolyl-BINAP (162 mg, 240 mmol). The vessel was then evacuated and filled with N_2, CH_2Cl_2 (30 mL) was added and the resulting red solution was stirred for 30 minutes. A sample of $AgSbF_6$ (41.2 mg, 0.12 mmol) was added under a stream of N_2 and the resulting cloudy solution was stirred for 24 h. The reaction mixture was eventually filtered through Celite under N_2 to give a clear orange solution, from wich the volatiles were removed under reduced pressure. The resulting orange powder was dried in vacuo for 1 h.

247 mg; yield = 87%

^{1}H-NMR (400 MHz, $CDCl_3$):

δ = 1.02 (d, *J* = 6.8 Hz, 3H), 1.32 (d, *J* = 6.8 Hz, 3H), 1.85 (s, 3H), 3.00 (m, 1H) (signals due to aromatic protons are omitted).

^{31}P-NMR (75 MHz, $CDCl_3$):

δ = 25.28 (d, ^2J = 61 Hz), 39.10 (d, ^2J = 62.6 Hz).

5.6 General procedure for catalytic Baeyer-Villger oxidations with aluminium (GP5)

In a standard procedure, a solution of Me_2AlCl in hexanes (0.10 mL 1.0 M, 0.10 mmol) was injected to enantiopure BINOL (29 mg, 0.10 mmol) in toluene under an argon atmosphere. Gas evolution was observed during the addition. After 45 min of stirring at ambient temperature, the ketone (0.2 mmol) was added to the suspension, which within an additional 15 min at RT became less turbid. The mixture was cooled down to –25 °C before the addition of cumene hydroperoxide (57 mg, 0.3 mmol) and then let warm to RT again. After 12 h of stirring the mixture was treated with 0.5 M aqueous HCl (4 mL), then diluted with MTBE, washed with saturated aqueous solution of $NaHCO_3$ and brine and finally dried over $MgSO_4$. The obtained solution was directly subjected to GC analysis for the determination of the conversion (calculated from area percentages in the GC) and *ee* (using chiral columns). When yields were to be determined, 1 to 2 mmol of ketone were employed and the product was purified by column chromatography on silica gel.

5.7 General procedure for the Baeyer-Villiger oxidation in $scCO_2$ (GP6)

Working with CO_2 involved the use of high pressure equipment. Basically the system consisted of a high pressure stainless steel autoclave whose size varied from 4 mL to 225 mL. The design had two opposite thick glass windows inserted into the walls of the autoclave to allow visual control of the reaction mixture. It was also equipped with two thermocouples to measure the inner temperature and the temperature of the electrically heated wall, needle valve and pressure transducer. The reactor was filled with CO_2 using a compressor. Dioxygen was then introduced from a pressurized vessel and the amount of O_2 was estimated from a pressure drop in the reservoir. The partial pressure of O_2 in the mixture was reckoned by means of calibration curves.

The reactions were performed in a stainless steel high pressure reactor (25 mL) equipped with thick walled glass windows. In a typical experiment, the ketone (1 mmol), the aldehyde (3 mmol) and a weighted amount of CO_2 (9 g) were introduced into the reactor.

The reactor was then charged with O_2 from a storage vessel, whereby the partial pressure was controlled by the use of calibration curves. The reaction mixture was stirred at the appropriate temperature (the temperature was controlled by means of a thermo couple). After 18 h, the autoclave was cooled to RT and then carefully vented through a cryo-trap (acetone-dry ice, –50 °C) to collect the product. The autoclave and the trap were washed with MTBE and the combined samples were directly submitted to GC and GC-MS analysis (*n*-decane was used as internal standard).

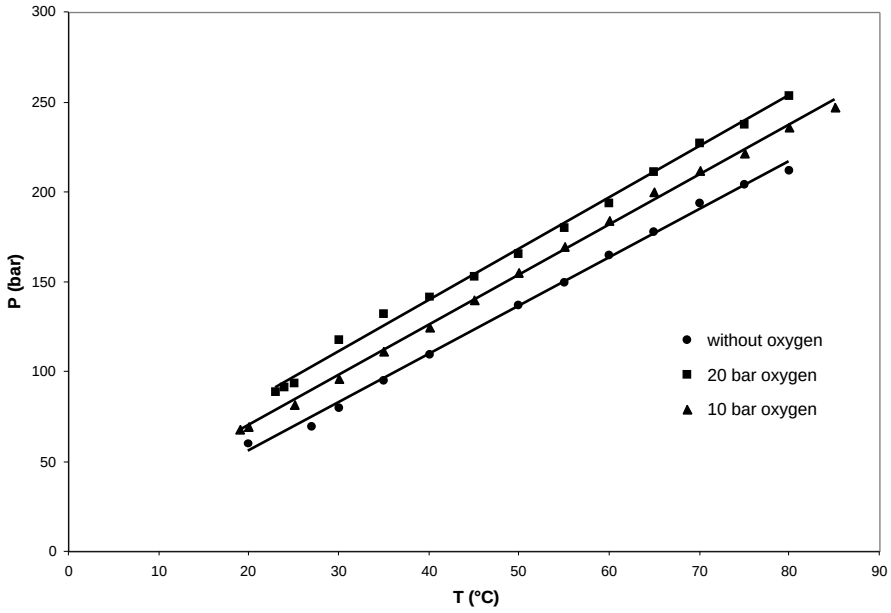


Figure 18 Calibration curves of the CO_2 partial pressure

5.8 In situ IR experiments

The spectra were recorded using an ASI/ Mettler Toledo REACT IR 1000 with different intervalls between the acquisition instances, each acquisition instance comprising 32 scans and a resolution of 8 cm^{-1}. Background spectra of each reaction component, i.e. toluene, (*S*)-BINOL, the metal source and the substrate, respectively, were recorded first. The sequence of periodic acquisition was started when the oxidant was injected into the reaction mixture.

6 Index of abbreviations

Ar	aryl
atm	1 atmosphere = 1.013 bar
BCDC	*N*-benzylcinchonidinium-chlorid
BINAP	2,2′-bis(diphenylphosphino)-1,1′-dinaphthyl
BINOL	2,2′-dihydroxy-1,1′-dinaphthyl
BIPOL	2,2′-dihydroxy-1,1′-diphenyl
Bn	benzyl
Bp	boiling point
Bu	butyl
c	concentration, [*c*] = 1 g / 100 mL
CHP	cumene hydroperoxide
d	day
DEP	*Direct Exposure Probe*
DET	diethyltartrate
DIP	*Direct Injection Probe*
DIPT	di-*iso*-propyltartrate
DMF	*N*,*N*-dimethylformamid
ee	*Enantiomeric Excess* − Enantiomerenüberschuss
Et	ethyl
Equiv	equivalent
GC	gaschromatography
h	hour
HPLC	*High Performance Liquid Chromatography*
HV	high vacuo
IR	infrared spectroscopy
M	molarity
M	metal, metal centre
MCPBA	*m*-chloroperbenzoic acid
Me	methyl
min	min
Mp	melting point

MS	molecular sieves
NMR	nuclear magnetic resonance
OTf	triflate, trifluormethansulfonate
Ph	phenyl
Pr	propyl
rac	racemic
R	organic rest
RT	room temperature
sc	*supercritical*
SCF	*supercritical Fluid*
SCWO	*Supercritical Water Oxidation*
TADDOL	*trans*-2,3-bis(hydroxydiphenylmethyl)-1,4-dioxaspiro[4.4]nonan
THF	tetrahydrofurane
TMEDA	*N*,*N*,*N*′,*N*′-tetramethylethylendiamine
TMS	trimethylsilyl
TOF	*Turnover Frequency*
TBHP	*tert*-butylhydroperoxide
TPFPP	5,10,15,20-tetrakis(pentafluorphenyl)porphyrin
VAPOL	*Vaulted Biphenanthrol* − 2,2′-dihydroxy-10,10′-diphenyl-1,1′-diphenanthryl

7 Publications

C. Bolm, O. Beckmann, C. Palazzi
Chiral aluminum complexes as catalysts in asymmetric Baeyer-Villiger reactions of cyclobutanones
Can. J. Chem. **2001**, *79*, 1593.

C. Bolm, O. Beckmann, A. Cosp, C. Palazzi
Enantioselective Baeyer-Villiger oxidations catalyzed by chiral magnesium complexes
Synlett **2001**, *9*, 1461.

C. Bolm, O. Beckmann, T. Kühn, C. Palazzi, W. Adam, P. B. Rao, C. R. Saha-Möller
Influence of hydroperoxides on the enantioselectivity of metal-catalyzed asymmetric Baeyer-Villiger oxidations and epoxidations with chiral ligands
Tetrahedron: Asymmetry **2001**, *12*, 2441.

C. Bolm, C. Palazzi, G. Franciò, W. Leitner
Baeyer-Villiger oxidation in compressed CO_2
Chem.Commun. **2002**, 1588.

Lectures

3. Nikolaus-Symposium of the Graduiertenkollegs 440
Aluminum-catalyzed Baeyer-Villiger oxidation
RWTH Aachen (DE), December 2000

Bayer Doktorandenkurse 2001
Magnesium-catalyzed asymmetric Baeyer-Villiger oxidation
Bayer AG, Leverkusen (DE), July 2001

„Excuposium“ organized by the Graduiertenkollegs 440
Co-operative effects in the asymmetric catalysis of Baeyer-Villiger reactions
DSM, Heerlen-Geleen (NL), September 2001

3. Workshop of the Graduiertenkollegs, Universität Leipzig
Metal-catalyzed asymmetric Baeyer-Villiger oxidation
Leipzig (DE), November 2001

223rd ACS National Meeting
Asymmetric Baeyer-Villiger oxidation
Orlando, Florida (USA), April 2002

Poster presentations

ISCH 12 Stockholm (SE) 2000
Enantioselective Al-mediated Baeyer-Villiger oxidation of cyclobutanones
C. Bolm, O. Beckmann, C. Palazzi

ORCHEM Bad Nauheim (DE) 2000
Al-promoted asymmetric Baeyer-Villiger reaction
C. Bolm, O. Beckmann, T. Kühn, C. Palazzi

SFB 347 – Symposium Würzburg (DE) 2000
Main group metal-mediated Baeyer-Villiger oxidation
C. Bolm, O. Beckmann, A. Cosp, C. Palazzi

Frontiers in Homogeneous Catalysis, Eindhoven (NL) 2000
Gemeinsame Tagung des NIOK und des Katalyseverbunds NRW
Main group metal-mediated Baeyer-Villiger oxidation
C. Bolm, O. Beckmann, A. Cosp, C. Palazzi

Bayer Doktorandenkurse, Leverkusen (DE) August 2001
Asymmetric metal-mediated Baeyer-Villiger oxidation
C. Bolm, O. Beckmann, C. Palazzi

Euregionale, Aachen (DE) 2002
Baeyer-Villiger oxidation in compressed CO_2
C. Palazzi, C. Bolm, G. Franciò, W. Leitner

8 CURRICULUM VITAE

Name	Chiara Palazzi
Place of birth	Venice, Italy
Date of birth	18th November 1971
Nationality	Italian

HIGHER EDUCATION

1990	Studies in industrial chemistry at the University „Cà Foscari“ of Venice Focus on chemical engineering and catalysis
03/1997	Diploma work in the research group of Prof. Dr G. Strukul Title: *Baeyer-Villiger oxidation of ketones with hydrogen peroxide catalyzed by Pt(II) hydroxo complexes: improvement of the nature and separability of the catalyst*
04/1998	Degree (Laurea) in industrial chemistry, University of Venice, Italy
05/1998	Qualifying examination as an official “Chemist“ in Italy
05/1998- 09/1999	Post-graduate fellowship with Prof. Dr G. Strukul at the Department of Industrial Chemistry, University of Venice Project: *Synthesis and reactivity of new silica-supported zirconia as oxidation catalysts with hydrogen peroxide as oxidant*
10/1999-09/2002	PhD studies on *Metal-based asymmetric catalysis in Baeyer-Villiger oxidations* at the Institute for Organic Chemistry, RWTH Aachen, under the supervision of Prof. Dr C. Bolm
10/1999-09/2002	Member of the DFG-Graduiertenkolleg 440 “Methods in asymmetric synthesis”