Asymmetric Anhydride Opening: Optimization and Applications

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1 Introduction

The demand for chiral molecules has increased considerably in recent years and intensive research has been carried out in order to develop improved methods for synthesizing such compounds. For many decades enantiomerically enriched molecules were generated either *via* classical resolution or by chemical transformation of an enantiomerically enriched precursor obtained with the help of chiral auxiliaries. It was as early as 1848 when the first resolution, that of tartaric acid, was carried out by Louis Pasteur.[1] With microscope and tweezers, he carefully separated the two mirror-image crystal forms of the sodium ammonium salt of optically inactive tartaric acid. The technique is laborious and requires the two crystal forms to be distinguishable. Unfortunately this does not happen very often and therefore new approaches for resolving the enantiomers have been developed. The most widely used method is based on converting the enantiomers of a racemic mixture into a pair of diastereomers which can be easily separated by crystallization or chromatographic methods, followed by an appropriate chemical transformation to liberate the enantiomers and recover the resolving agent. An emerging technology is the separation of the racemic mixture by chiral high-performance liquid chromatography by using a chiral stationary phase. One drawback of all resolution techniques is that the desired enantiomer can only be isolated in up to 50% yield. Enantioselective synthesis using auxiliaries requires stoichiometric amounts of chiral substances which are not incorporated in the target molecules and have to be removed after the establishment of the stereogenic centers. Asymmetric transformations, where achiral starting materials are converted into enantiomerically enriched products with the help of a chiral catalyst or mediator have, therefore, significant potential advantages over the afore mentioned approaches. Effective catalysts for several processes are readily available in nature (biocatalysis) or they have been designed and synthesized in laboratories (chemical catalysis). Enzymes are the catalysts which evolved in nature and one of their features is their high selectivity while conducting the reactions.[2] One limitation of the enzymatic processes is that most of the time only one enantiomer of the product can be obtained directly. Over the last few years, considerable efforts have been made in the field of

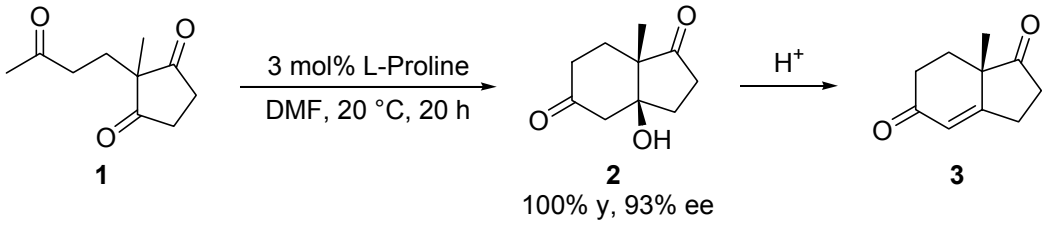
organometallic catalysis and a wide variety of catalytic transformations are leading to products with >99% ee. A major advance was achieved in the 1970's by Knowles and his colleagues,[3] who performed the first enantioselective hydrogenation of a prochiral olefin, with up to 96% ee in the presence of a rhodium based catalyst. The process was immediately commercialized and applied on a large scale in the synthesis of the anti-Parkinson drug L-DOPA (95% ee).[4] In recognition of his achievements, Knowles[5] shared the 2001 Nobel Prize in chemistry with Noyori for enantioselective hydrogenation[6] and Sharpless for enantioselective oxidation catalysis.[7] All these processes have found industrial applications in the synthesis of chiral drugs and building blocks for asymmetric synthesis. Thus, often the concept of asymmetric catalysis is connected with that of metal-complex catalyzed syntheses and much work in this area has been focused on the design and synthesis of such organometallic complexes which are able to induce asymmetry during the transformations. Recently, scientists have also become more interested in the possibility of using simple organic molecules to induce chirality in the products. Actually, several popular organocatalysts are well known ligands in the field of organometallic chemistry. Their rediscovery and use as catalysts themselves had a considerable impact on the modern organic chemistry and the field of asymmetric organocatalysis is a rapidly growing one. So far, the common catalysts involved in these processes are nitrogen-containing molecules such as amino acids and derivatives, small peptide chains, cinchona alkaloids as well as chiral diamines and heterazolium based compounds.[8] The scope of organocatalysis has been extended considerably and a large range of reactions are now performed efficiently in the presence of these small chiral molecules. Their great potential was demonstrated in the last two years when typical transition-metal-mediated coupling reactions were performed under metal-free conditions.[9] Organocatalysis now offers complementary approaches to the well-established chemical and biochemical transformations and some of their practical advantages are notable. The catalysts are inexpensive, easily available and usually more stable than the metal-based complexes. The reactions generally tolerate aerobic conditions and do not require absolute solvents. In comparison with enzymes, organocatalysts possess a wider substrate scope because, often, both enantiomeric forms of the chiral catalyst are readily accessible from nature or easily synthesized and modified by simple chemical reactions.

Furthermore, they can be anchored to a solid support, easily recovered after the transformations, and repeatedly reused without loss of selectivity.

If in the case of metal-mediated enantioselective catalytic reactions, the metal is the one responsible for the transmission of chiral information through the formation of a favorable transition state, in its absence, the transition state necessary for enantioselective transformation is achieved either through passive or dynamic interactions. Dynamic bindings involve activation of the substrate through nucleophilic addition of the chiral amine catalyst to the prochiral substrate. Such bindings also rely on the formation of hydrogen bonding between substrate and catalysts to aid stereoselectivity. Organocatalysts, which function using passive (hydrophobic, van der Waals, electrostatic interactions) or dynamic interactions, display characteristic features and mechanistic similarities to known bioorganic catalysts and are often referred to as enzyme mimetics. Generally, the organocatalysts proved to be highly effective with a wide range of substrates in different reactions and therefore deserve their recognition as a privileged class of ligands. For example proline[10] and its derivatives are known to effectively catalyze different types of reactions such as the intra- and intermolecular aldol reaction, Michael addition, Mannich reaction, [4+2] cycloaddition, Baylis-Hillman reaction, as well as α-alkylation and α-amination of aldehydes.[11] Cinchona alkaloids further enlarge the field of organocatalysis and remarkable results have been achieved in the field of anhydride desymmetrization, conjugate addition, ketene chemistry and kinetic resolution.[12]

1.1 Proline

Even if the first attempts to use pure organic molecules as chiral catalysts date back from the beginning of the twentieth-century, the first successful results were not obtained until the early 1970s by Hajos and Parrish,[13] as well as Eder, Sauer and Wiechert[14] independently. The two groups have discovered that asymmetry could be induced in a Robinson type annulation of an achiral triketone **1** by simply adding a catalytic amount of D- or L-proline to the reaction mixture (Scheme 1).

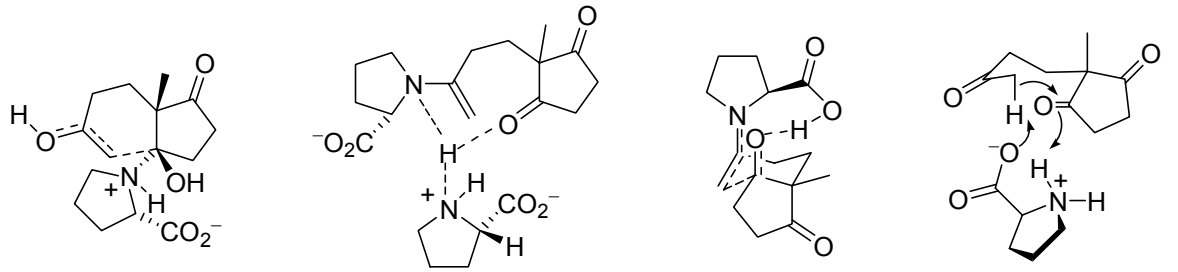


1 **2** **3**

100% y, 93% ee

Scheme 1: Hajos-Parrish-Eder-Sauer-Wiechert Reaction.

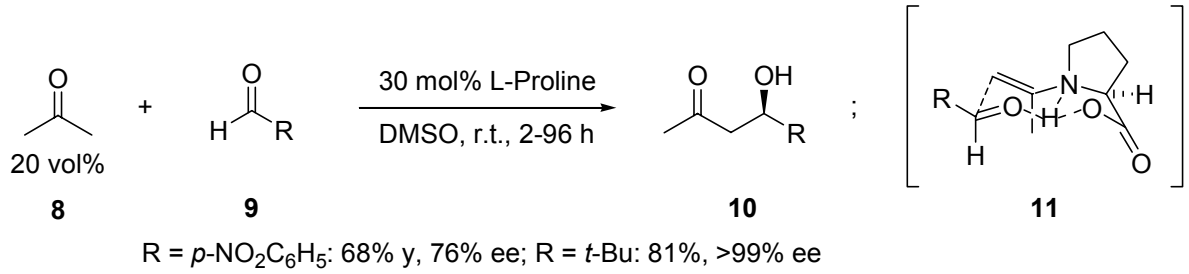
The first mechanistic hypotheses were suggested also by Hajos in 1974. Upon observation that no O-18 was incorporated into the product when the reaction was carried out in the presence of O-18 enriched water, Hajos and Parrish proposed that proline activates one of the two enantiotopic carbonyl acceptor groups by forming a carbinol amine **4** in the transition state (TS). Thirteen years later, Agami and co-workers published strong evidence (second order in proline, small negative nonlinear effect) for an enamine type intermediate and propose a TS **5** which involves two proline molecules.[15] Recently, after taking a deeper look on the possible products of this reaction, Houk[16] proposed a set of four TS's, (two chair and two boat conformations), and with the help of density functional theory calculations they concluded that the chair TS's are lower in energy than the boat TS's. Of the two chair TS's, the energy barrier of the one responsible for the formation of the (*S*,*S*) bicyclic ketol is lower than the barrier for the formation of the (*R*,*R*) product, a result which is in agreement with the experimental data. Swaminathan invoked a heterogeneous aldolization process which takes place on the surface of crystalline proline (TS **7**).[17]



4 Hajos Model **5** Agami Model **6** Houk Model **7** Swaminathan Model

Scheme 2: Selected TS Models for the Proline-Catalyzed Aldol Reaction.

Recently, List, Lerner and Barbas have developed the first intermolecular version of a cross-aldol reaction between aldehydes as acceptors and ketones as donors using catalytic amounts of proline.[18] While aromatic aldehydes gave products with moderate selectivity (~70% ee),[18a] a large variety of α-mono- and α-disubstituted aliphatic aldehydes provided aldols with excellent enantioselectivities (up to 99% ee, Scheme 3).[18b] Under optimized conditions, it can also be applied to α-unbranched aliphatic aldehydes to give products with up to 99% ee. Previously, the use of α-unbranched aldehydes in the cross-aldolization process was hindered by their self-condensation, fact which can be avoided now by carrying out the reactions under optimal conditions. List's kinetic and theoretical studies on intra- and intermolecular versions of the reaction contradict Hajos and Agami's findings and point to a unified enamine catalysis mechanism.[19] List's observations are consistent with Houk's theoretical calculations, and the proposed metal-free Zimmerman-Traxler-type transition state **11**[20] invokes one single proline molecule which catalyses the reaction in the same manner as type I-aldolases and catalytic antibodies (type I-aldolase mimics) do.[21]



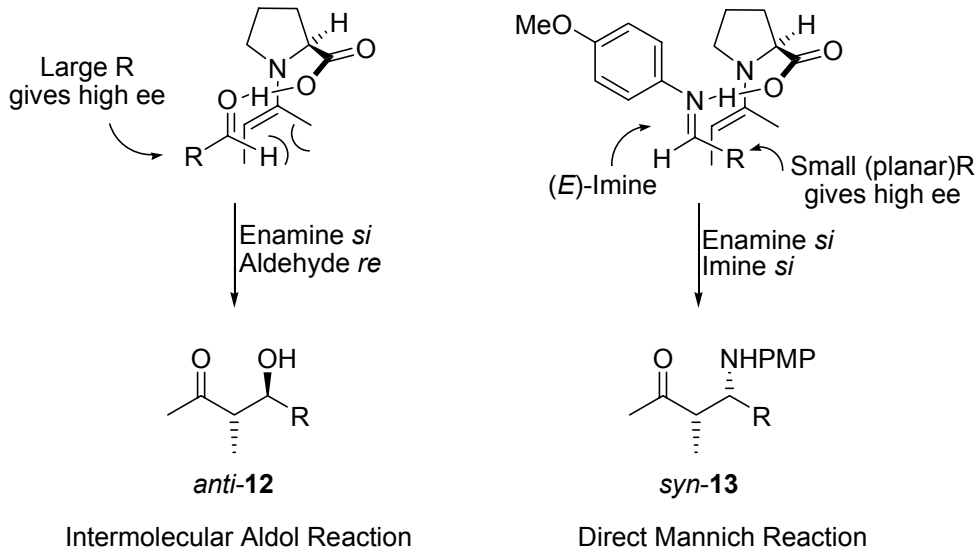
R = *p*-$NO_2C_6H_5$: 68% y, 76% ee; R = *t*-Bu: 81%, >99% ee

Scheme 3: Proline Mediated Intermolecular Aldol Reaction.

MacMillan further enlarged the substrate scope by demonstrating that α-unbranched aldehydes can be used as donors in the reaction with aldehyde acceptors to give products in high yields with up to 24:1 dr and >99% ee.[22] Cordova reported the proline catalyzed direct asymmetric cross-aldol reaction of aldehydes in an ionic liquid medium, leading to optically pure 3-hydroxy aldehydes (99->99% ee) in high yields (68-78%) and good diastereoselectivities (3:1 to >19:1 dr).[23]

An asymmetric intramolecular version of the Hajos-Parrish-Eder-Sauer-Wiechert reaction has also been developed, and the *enolexo* aldolization was successfully applied to various pentane-1,5-dialdehydes to give products in high yields and diastereoselectivities, with up to 99% ee.[24]

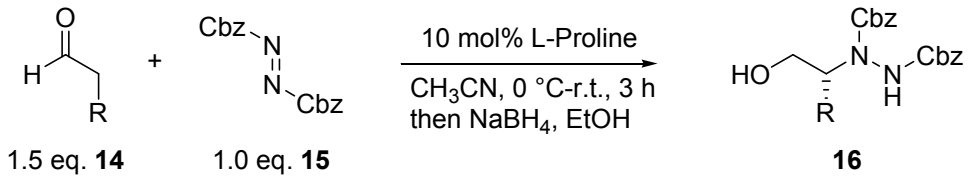
Fascinated by these results, the scientific community became increasingly attracted to these small molecules and the potential behind them. Soon after, it was found that proline is capable of performing other types of reaction in a highly selective manner. For example, the proline catalyzed Mannich reaction offers practical access to a large number of enantiomerically enriched β-amino carbonyl compounds.[25] Under optimized conditions, it can be carried out either directly, as a three-component one-pot reaction, or indirectly, using preformed imines and enolates. Various structurally diverse ketones and aldehydes have been tested in the reaction with different aniline derivatives to give products in high yields and excellent selectivities. The reaction is supposed to follow an enamine mechanism[26] and occurs with diastereo- and enantioselectivity opposite to that of related aldol reaction (Scheme 4).



Scheme 4: Proposed TS for Proline Catalyzed Aldol and Mannich Reactions.

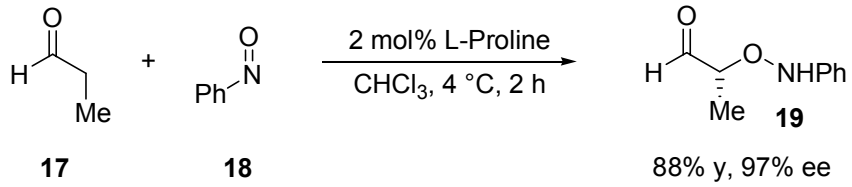
Surprisingly, only modest levels of enantioselection were achieved when L-proline was used as a catalyst in the asymmetric Michael addition of ketones to nitro olefins[27] and α-alkylation of aldehydes.[28] In contrast, excellent yields and selectivities

were achieved when L-α-methyl proline (10 mol%) was employed in the intramolecular alkylation reaction.[28] No detectable racemization, self condensation or catalyst alkylation occurs during this process which provides access to enantiomerically enriched cyclopropane, cyclopentane and pyrrolidine derivatives. Also worthy of note is the α-amination of ketones and aldehydes which furnishes useful precursors for the synthesis of 2-oxazolidinones and other natural and unnatural α-amino acids derivatives (Scheme 5).[29] A similar enamine mechanism is suggested to rationalize the stereochemical outcome of the reaction.



Scheme 5: Proline Catalyzed Asymmetric α-Amination of Aldehydes.

Recently, MacMillan, Hayashi, Zhong, and soon after Córdova, independently reported on the proline catalyzed enantioselective α-oxyamination of aldehydes.[30]

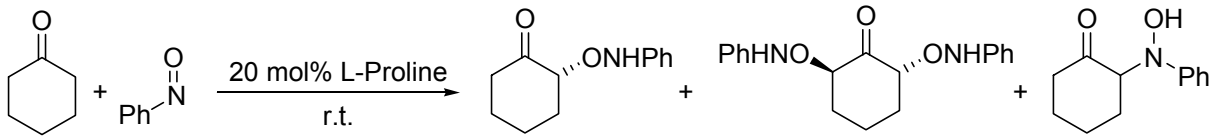


Scheme 6: Proline Catalyzed Asymmetric α-Oxyamination of Aldehydes.

MacMillan found that the use of chloroform as solvent and the superior reactivity of nitrosobenzene are suppressing the self-aldolization and α-amination pathways.[30a] Lowering the temperature to 4 °C also had a positive effect on the reaction selectivity and various aldehydes were enantioselectively oxidized in good yields under these mild conditions. In addition, lowering the catalyst loading from 10 to 0.5 mol% had no significant detrimental influence on the enantioselectivity. Accordingly, the oxyamination of propanal in chloroform at 4 °C in the presence of 2 mol% L-proline

afforded the α-aminooxy aldehyde in 88% yield and 97% ee. Zhong reported the *in situ* reduction of the carbonyl group of **19** to give the 1,2-protected diol (secondary alcohol protected as an *O*-amino group) with high enantioselectivity.[30b,c] Subsequent hydrogenation over Adams catalyst furnished the corresponding 1,2-diol without any loss in the optical purity. Accordingly, various aliphatic aldehydes were converted into the corresponding 1,2-protected diols with excellent selectivities (94-99% ee). Hayashi reported that the same reaction can be performed in acetonitrile at –20 °C to give the protected diol in quantitative yield (two steps) and 98% ee.[30d]

Excellent chemo-, regio-, and enantioselectivities were reported by Córdova in the α-oxyamination of cyclic, as well as acyclic ketones (Scheme 7).[30e,31]



20 **18** **21** **22** **23**

$CHCl_3$	91% y, >99% ee	-	-
DMSO	70% y, >99% ee	22% y, >99% ee	-
DMSO	70% y, >99% ee	-	-

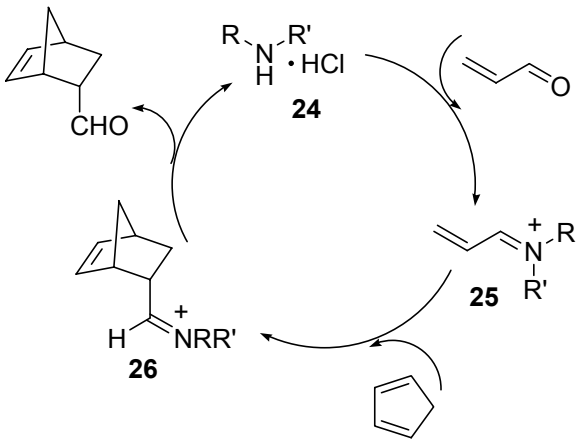
Scheme 7: Proline Catalyzed Asymmetric α-Oxyamination of Cyclic Ketones.

The double oxyamination of the ketones with two available enol forms could be circumvented by slow addition of the nitrozo electrophile, *via* syringe pump, to the reaction mixture. The oxyamination of the acyclic ketones afforded, along with the *O*-addition adducts (>99% ee), small amounts of the aminated ketones with the same regioselectivity as the major products. At the same time, Hayashi applied the same methodology to different cyclohexanone derivatives to give products in good yields and excellent selectivity (mainly >99% ee).[32]

1.2 Amino acid derivatives

1.2.1 Imidazolidinone derivatives

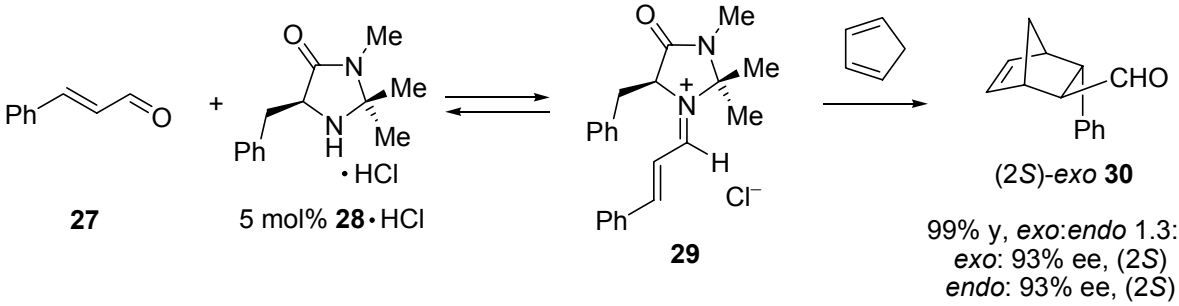
Several attempts towards the development of an organocatalytic asymmetric Diels-Alder reaction are described in the literature and chiral amines such as cinchona alkaloids, ephedrine, and prolinol derivatives are known to catalyze the reaction with a moderate level of enantioselectivity.[33] The first highly selective Diels-Alder reaction between α,β-unsaturated aldehydes and various dienes was reported by MacMillan[34] and employs the use of secondary amines (as their hydrochloric salts) as chiral catalysts. The strategy was based on the possibility of activating the dienophile by lowering its LUMO energy upon reversible formation of an iminium ion. This process is analogous to the Lewis acid catalyzed Diels-Alder reaction where an unsaturated carbonyl system is activated upon chelation. The general reaction mechanism is outlined in Scheme 8. The first step employs the formation of iminium ion **25** between catalyst and aldehyde. Next, Diels-Alder cycloaddition leads to the iminium ion **26** and subsequent hydrolysis provides the enantiomerically enriched product and liberates the catalyst **24**.



Scheme 8: Proposed Mechanism for the Organocatalyzed Diels-Alder Reaction.

Several catalysts were evaluated in the reaction between cinnamaldehyde (**27**) and cyclopentadiene and the best results were obtained with the phenylalanine derivative

28 (Scheme 9). Molecular modeling calculations explain the asymmetric induction of the reaction in terms of selective formation of the (*E*)-iminium isomer **29**, and by substantial shielding of the *re* face of the dienophile by the catalyst's benzyl group, leaving the *si* face exposed for cycloaddition.

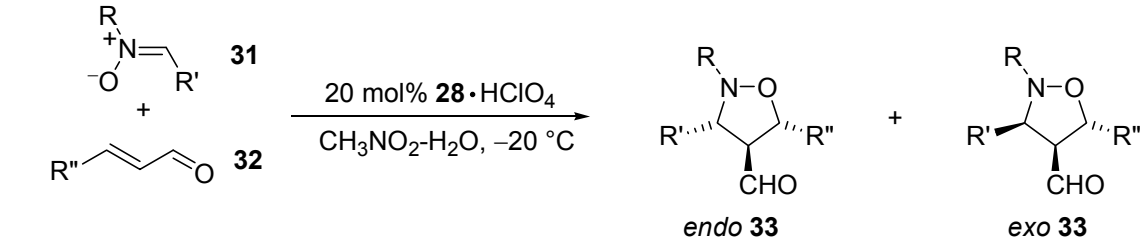


Scheme 9: Organocatalytic Diels-Alder Reaction.

The reaction proved to be general with respect to the structure of the diene and the dienophile, and the products were obtained in good yields and excellent enantioselectivities (83-96% ee), with *exo*:*endo* selectivities ranging from 1:14 to 35:1. The reaction could also be extended to α,β-unsaturated ketones by using a modified catalyst.[35] A large variety of simple cyclic and acyclic enones have been tested in reactions with different dienes, affording products with superior diastereo- and enantiocontrol compared to the metal catalysis pathway. The preparative utility of the method was demonstrated in the reaction between ethyl-vinyl ketone and different dienes, where *endo* products were isolated as single diastereomers (GLS- and HPLC-analysis) with up to 98% ee.

The same imidazolidinone **28**·HCl proved to be highly effective in the 1,3-dipolar cycloaddition between nitrones and α,β-unsaturated aldehydes.[36] Reaction at -10 °C between crotonaldehyde **32** (R" = Me) and nitrone **31** (R = Bn, R' = Ph) provided the isoxazolidine **33** in 70% yield with a 88:12 *endo*:*exo* ratio and 95% ee (*endo*). Variation of the Brønsted acid cocatalyst from HCl to $HClO_4$ led to an increase in the diastereoselectivity (94:6) and a slight decrease in the enantioselectivity (90% ee). However, the enantioselectivity decrease could be avoided by performing the reaction at lower temperature (-20 °C, 94% ee).

Scheme 10 gives an overview of a field where organocatalysis succeeded, while traditional Lewis-acid catalysis failed. Coordination of the Lewis-acid on the nitrone oxide in the presence of monodenate dipolarophiles inhibits the reaction, while the organocatalyst selectively activates the α,β-unsaturated aldehydes, enabling the reaction to take place.



R = Me, Bn, Allyl; R" = H, Me;
R' = 2-naph, *c*-hex, *p*-MeC_6H_4, *p*-$MeOC_6H_4$, *p*-ClC_6H_4, Ph.

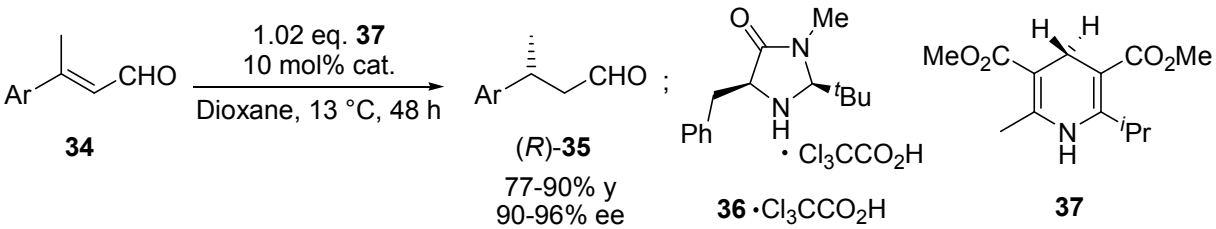
70-98% y, *endo* :*exo* 80:20 to 99:1
endo: 90-99% ee

Scheme 10: Organocatalyzed 1,3 -Dipolar Cycloaddition.

Recent studies have shown that the concept of iminium ion activation is a general strategy for the asymmetric organocatalysis and remarkable results were also achieved in the Friedel-Crafts alkylation,[37] conjugate addition of electron-rich benzenes to α,β-unsaturated aldehydes[38], aldol reaction,[39] 4+3 cycloaddition reactions,[40] as well as Mukaiyama-Michael reaction[41] and α-chlorination of aldehydes.[42] A more reactive and selective chiral imidazolidinone catalyst, in which the two geminal methyl groups were replaced by a *tert*-butyl group, was developed in order to ensure a high level of asymmetric induction for the conjugate additions and Mukaiyama-Michael reactions. Catalyst **28**·HCl was also found to selectively catalyze the intramolecular Michael reaction of aldehydes.[43] The reaction requires very mild conditions (THF, r.t., 15-24 h) and it is supposed to proceed through an enamine mechanism. This process affords cyclic ketoaldehydes in excellent yields and with high diastereo- and enantiomeric excesses.

One of the most useful chemical transformations developed in laboratories and employed on large scale in the synthesis of various chiral drugs, agrochemicals and natural products is the asymmetric hydrogenation. Statistically, hydrogenation of carbon-carbon double bonds and carbonyl compounds are predominant

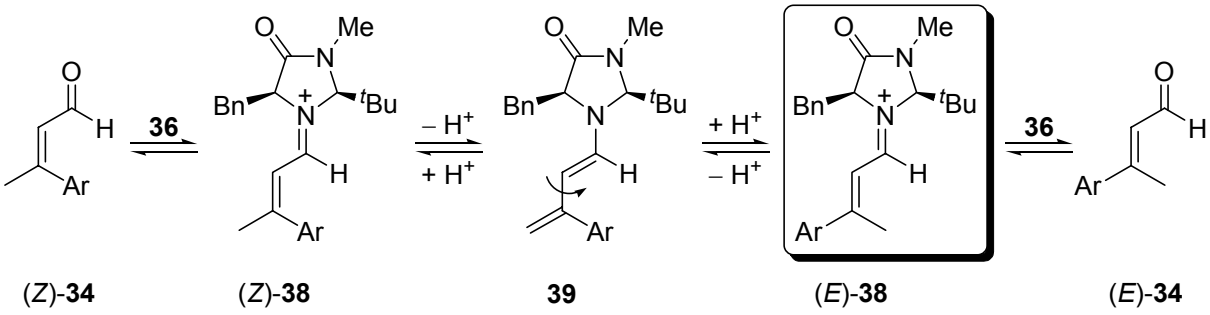
transformations applied in industry.[44] Up to now, almost all chemical reductions require metal catalysts or stoichiometric amounts of metal hydrides. Only few metal free asymmetric reductions of olefins have been reported in the literature and they are based on biological transformations.[45] In late 2004 List reported on the first metal free non-asymmetric transfer hydrogenation of olefins.[46] Diverse α,β-unsaturated aldehydes, including substituted aromatic and aliphatic ones, were chemoselectively reduced in the presence of Hantzsch ester as hydride donor and dibenzylammonium trifluoroacetate (5 mol%) as catalyst. The reaction was performed in THF at r.t. and required 5-6 h for complete conversion. No aldolization or carbonyl reduction could be detected and various functional groups, which are sensitive to standard hydrogenation conditions, were tolerated under these conditions. As expected, the first asymmetric version did not hesitate to appear. Independently, List[47] and MacMillan[48] have developed similar systems for the metal-free asymmetric reduction of olefins. Treatment of trisubstituted enals **34** with a slight excess of dihydropyridine **37** and a catalytic amount of MacMillan's catalyst **36** (dioxane, 13 °C) affords, after 48 h, the corresponding saturated aldehydes **35** in high yields and selectivities (Scheme 11).



Scheme 11: Organocatalytic Conjugate Reduction of α,β-unsaturated Aldehydes according to List.

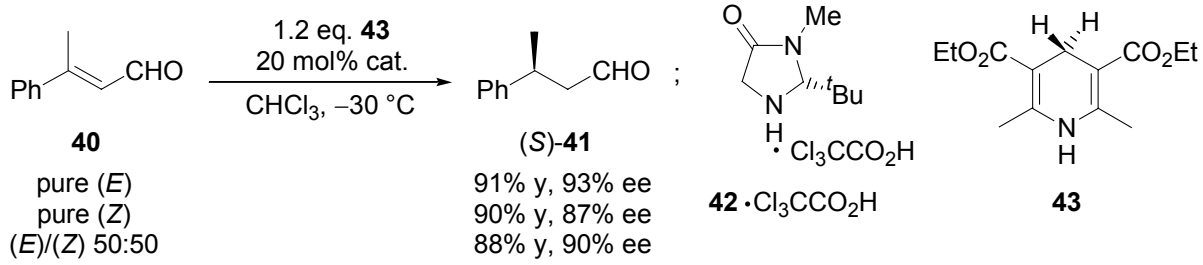
In order to study the influence of the double bond geometry on the stereochemical outcome of the reaction, pure (*E*)- and (*Z*)-3-(4-nitrophenyl)but-2-enal were subjected to the same reaction conditions and in both cases the same (*R*)-3-(4-nitrophenyl)butanal was isolated in good yield and 94% ee. Similarly, different (*E*)/(*Z*) substrate mixtures always afforded the same (*R*)-isomer with 94% ee. The reaction is supposed to follow an iminium mechanism and to proceed in all cases (pure and mixture of isomers, respectively) *via* an iminium ion (*E*)-**38**. During the reaction, the

(*Z*)-**38** intermediate easily isomerizes to (*E*)-**38** and the proton transfer from the dihydropyridine **37** to (*E*)-**38** occurs much faster than that to (*Z*)-**38** (Scheme 12).



Scheme 12: Proposed Mechanism for the Organocatalytic Asymmetric Transfer Hydrogenation.

Various α,β-unsaturated aldehydes were selectively reduced under these conditions to give products in high yields and enantioselectivities (77-90% y, 90-96% ee).
High levels of enantiocontrol (91-97% ee) were also attained by MacMillan, for the same olefin reduction. After screening different reaction conditions, MacMillan concluded that the reduction of enal **40** with Hantzsch ester (**43**) is highly efficient when the reaction is catalyzed by imidazolidinone **42**·Cl_3CCOOH at low temperature in chloroform.

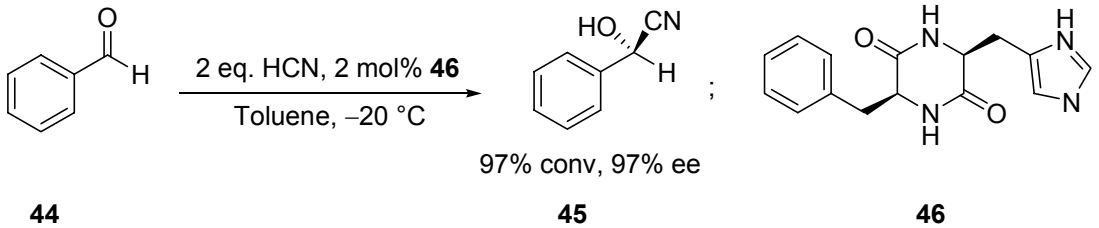


Scheme 13: Organocatalytic Olefin Reduction According to MacMillan.

Remarkable, the two systems complement each other in terms of product stereochemistry. Comparison of Scheme 11 with 13 shows that either enantiomer of the saturated aldehydes is readily available from the same starting material by appropriate selection of the catalyst. Notable is also the fact that both processes are enantioconvergent in that the same enantiomer is obtained independent of the olefin geometry.

1.2.2 Peptide-based catalysts

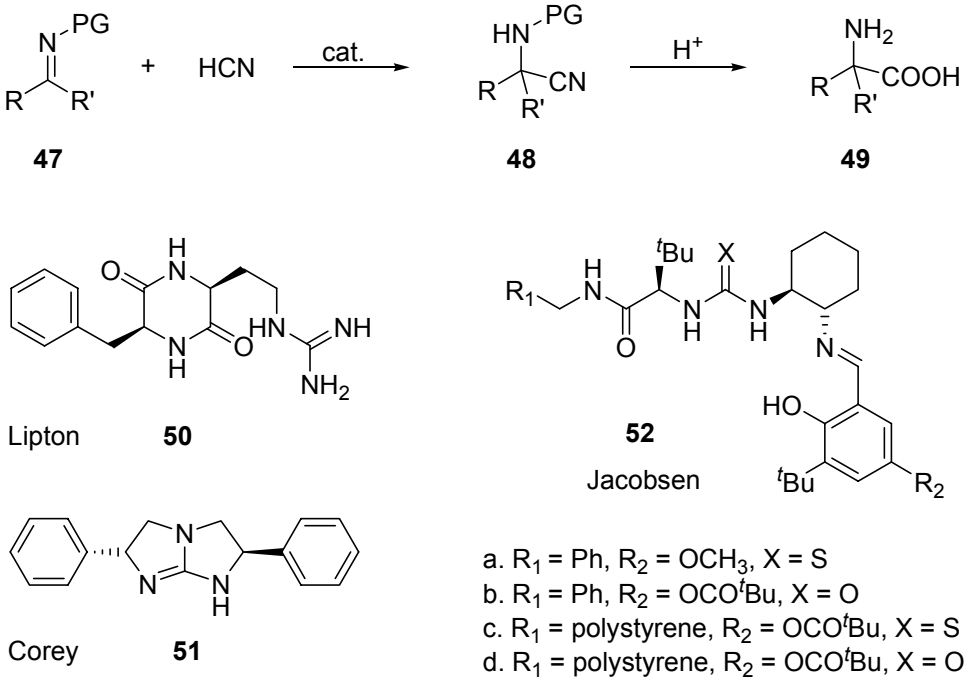
The hydrocyanation of aldehydes[49] is one of the first reactions which involves the use of an oligopeptide as catalyst.[50] Oxynitrilase (hydroxynitrile lipase) is known to catalyze the stereospecific addition of HCN to aldehydes and to alkyl methyl ketones, as well as the transhydrocyanation of aromatic and aliphatic aldehydes with acetone cyanohydrin.[51] Enantiomerically enriched cyanohydrins are easily prepared on kg scale just by using small quantities of the corresponding enzyme. Inoue[52] has designed alternative synthetic catalysts for the anhydride hydroxycyanation and the best results were obtained with the cyclic diketopiperazine **46**. Electron rich aromatic aldehydes proved to be the best substrates for this reaction. In contrast, electron deficient aromatic aldehydes gave products with lower enantioselectivities. The reaction of aliphatic and heteroaromatic aldehydes also proceeded with moderate to high levels of asymmetric induction. Solvent and catalyst preparation were crucial factors in obtaining high yields and selectivities. Use of an amorphous catalyst and toluene, which produces a gel-like reaction mixture, resulted in higher selectivity than that obtained with a crystalline catalyst structure and protic solvents or additives.[52,53] Accordingly, cyclic peptide **46** catalyzes the stereospecific addition of HCN to the *si*-face of benzaldehyde (**44**) to give (*R*)-2-hydroxy-2-phenylacetonitrile (**45**) with 97% conversion and 97% ee. Under optimal conditions, cyanohydrin **45** was next converted, without loss of enantiomeric excess, into (*R*)-mandelic acid, (*R*)-methyl mandelate and (*R*)-2-amino-1-phenylethanol,[52] known useful reagents in organic chemistry.



Scheme 14: Hydrocyanation of Aldehydes According to Inoue.

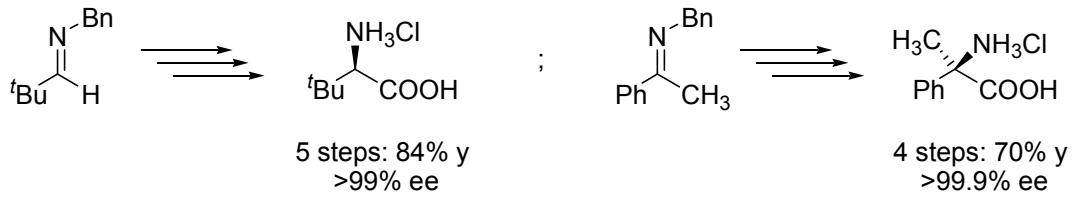
Since several mechanistic similarities between the hydrocyanation of aldehydes and imines are known, the next step was to test catalyst **46** in the asymmetric Strecker

synthesis.[54] Surprisingly, no asymmetric induction could be achieved with diketopiperazine **46**.[55] A slight modification of the catalyst, involving replacement of the imidazole side chain with a more basic guanidine group, afforded a new catalyst **50**, which promoted an enantioselective reaction. This slight modification of the Inoue's catalyst resulted in opposite facial selectivity for HCN addition and the (*S*)-isomer was isolated as major product in all cases. Addition of HCN to preformed *N*-benzhydryl protected imines, subsequent hydrolysis of the nitrile and *N*-deprotection yields optically active α-amino acids. While aromatic aldimines (R = Ar, R' = H) afforded products with up to 99% ee, aliphatic (R = Alkyl, R' = H) and electron deficient (R = 3-nitrophenyl, R' = H), as well as heteroaromatic derivatives afforded almost racemic products. In order to circumvent this problem, new peptide-based catalysts were synthesized and optimized by means of combinatorial chemistry.[56] Two ligand libraries (48 + 132 members) were screened in the asymmetric Strecker reaction (addition of a silyl ketene acetal to *N*-Boc benzaldimine)[56a] and the best results were achieved with **52**-urea and thiourea derivatives. Remarkable, with **52b** as catalysts, the reaction was successful for a broad range of aryl and alkyl aldimine-substrates, as well as for various ketimines.



Scheme 15: Novel Organocatalysts for the Asymmetric Strecker Reaction.

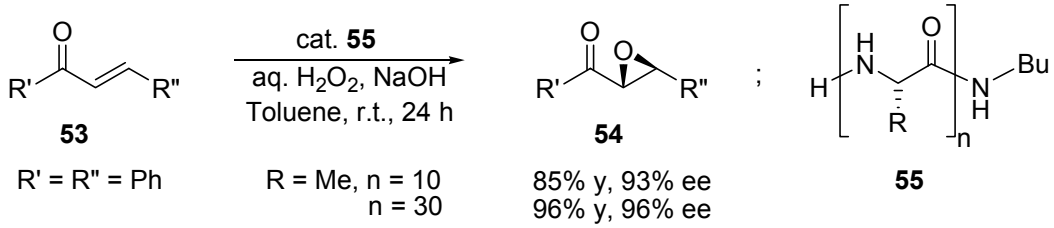
The efficiency of the process was demonstrated by the synthesis of two optically active α-amino acids (Scheme 16). Unnatural (*R*)-*tert*-leucine[56b] and (*R*)-α-methyl phenylglycine[56c] were isolated in good overall yields with >99% ee.



Scheme 16: Applications of the Organocatalytic Strecker Reaction in the Synthesis of Optically Pure α-Amino Acids.

Chiral C_2-symmetric guanidine **51**, derived from (*R*)-phenylglycine, promoted the addition of HCN to *N*-protected aldimines, yielding the corresponding α-amino nitriles in high yields (80-99%) and with moderate to high selectivities (50-80% ee).[57] Hydrogen bonding and van der Waals interactions between the catalyst and the imine are taken in consideration in order to explain the reaction selectivity.
Overall, the reactions described above offer attractive alternatives for the synthesis of optically active amino acids.

In 1980, Juliá reported on the asymmetric epoxidation of chalcone **53** (R' = R" = Ph) in a triphasic system consisting of an aqueous solution of NaOH and H_2O_2, a solution of chalcone in an organic solvent and an insoluble poly-α-amino acid as catalyst.[58] Toluene, excess NaOH-H_2O_2 and polypeptides with more than 10 amino acids in the chain were found to have a positive effect on the yield and enantioselectivity.[59] The process has been optimized and several oxidant systems and catalysts have been developed in order to ensure shorter reaction time, a larger substrate spectrum and to prevent the catalyst degradation.[59,60,61] Epoxides generated by using Juliá-Colonna reaction are useful intermediates in the synthesis of optically active compounds such as: δ-lactones,[62] 2,3-*trans*-disubstituted tetrahydroquinolones[63] and 2-arylpropanoic acids including the non-steroidal anti-inflammatory agent (S)-fenoprofen.[64]



Scheme 17: Juliá-Colonna Epoxidation of Enones.

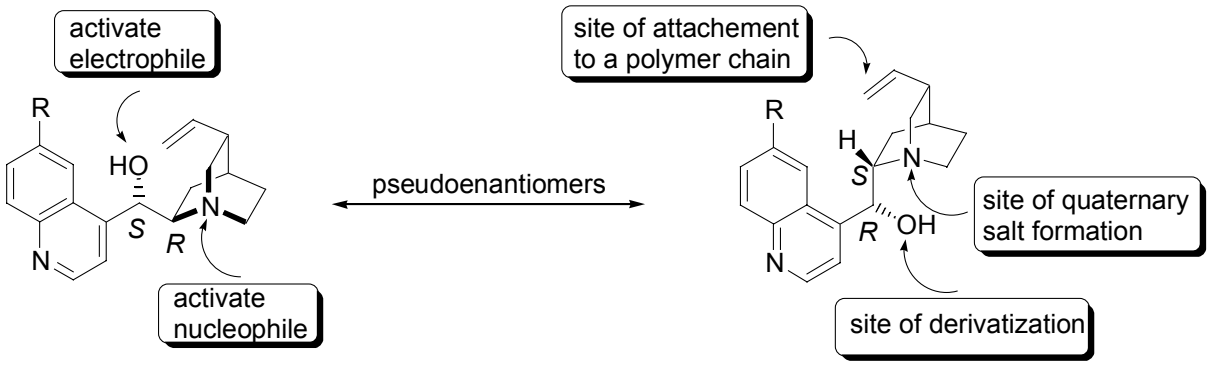
Recently, the Juliá-Colonna epoxidation was further optimized to make it applicable for large-scale industrial applications.[60e]

1.3 Cinchona alkaloids

Naturally occurring cinchona alkaloids constitute our next privileged class of catalysts and ligands for asymmetric synthesis. Among all known alkaloids, they are the most widely used compounds in the pharmaceutical, chemical and food industry. Several hundred tons of cinchona alkaloids are produced annually by extraction from the bark of the cinchona tree. Their family consists of four pairs of pseudoenantiomers: quinine (**QN**) – quinidine (**QD**), cinchonidine (**CD**) – cinchonine (**CN**) as well as the corresponding hydrogenated analogs.

Although known to treat malaria since the beginning of the 17th century,[65] the alkaloid quinine was isolated for the first time from the cinchona bark in 1820.[66] Since then, several studies have been done in order to elucidate the structure of quinine and its correct stereochemistry and several attempts toward an asymmetric total synthesis have been reported.[67] Nevertheless, the first stereoselective total synthesis of quinine was accomplished only five years ago.[68] More recently two other successful approaches, including a catalytic version, and leading to both pseudoenantiomers (**QN**, **QD**), have been reported.[69] Due to their ready availability, stability and low production cost, cinchona alkaloids have been used frequently as resolving agents. Within the last few years they impose also as efficient catalysts for a large range of reactions. Their main advantages are that they posses a naturally occurring

(pseudo)enantiomeric counterpart, and that their structure can be easily modified in order to obtain a more effective catalyst.



QD Quinidine **56** | R = OMe | **QN** Quinine **58**

CN Cinchonine **57** | R = H | **CD** Cinchonidine **59**

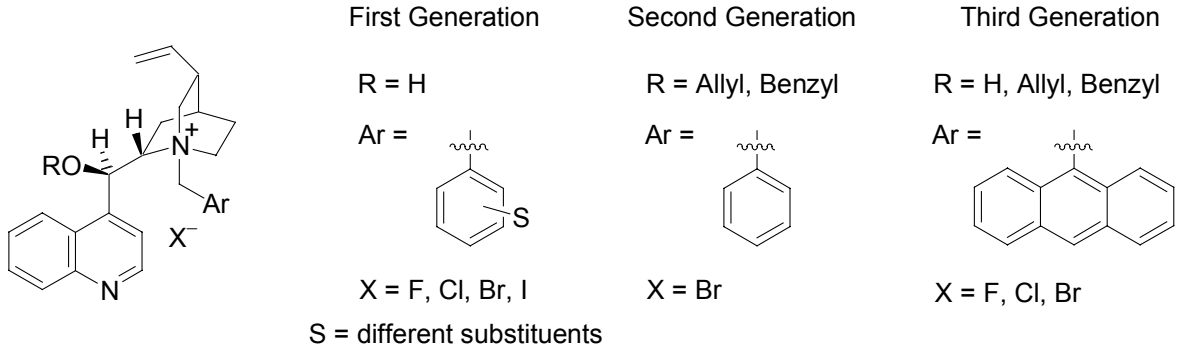
Scheme 18: Schematic Representation of the Common Cinchona Alkaloids.

1.3.1 Carbon-carbon bond formation

1.3.1.1 Alkylation reactions

Phase-transfer catalysis (PTC) is an attractive alternative for the reactions taking place in two- or three-phase systems and involving anionic intermediates. Crown ethers, cryptands, open chain polyethers and quaternary onium salts (phosphonium and ammonium salts) promote these types of reaction by facilitating the transfer of species from one reaction phase to another and so, making the reaction between reagents in two/three non-miscible phases possible. The most popular catalysts applied in the asymmetric PTC are chiral, quaternary ammonium salts. Among them, cinchona alkaloid derivatives have proved to be efficient over a large range of reactions. In this respect, cinchonine and cinchonidine derivatives have been used extensively in enantioselective alkylation reactions. After several studies it turned out

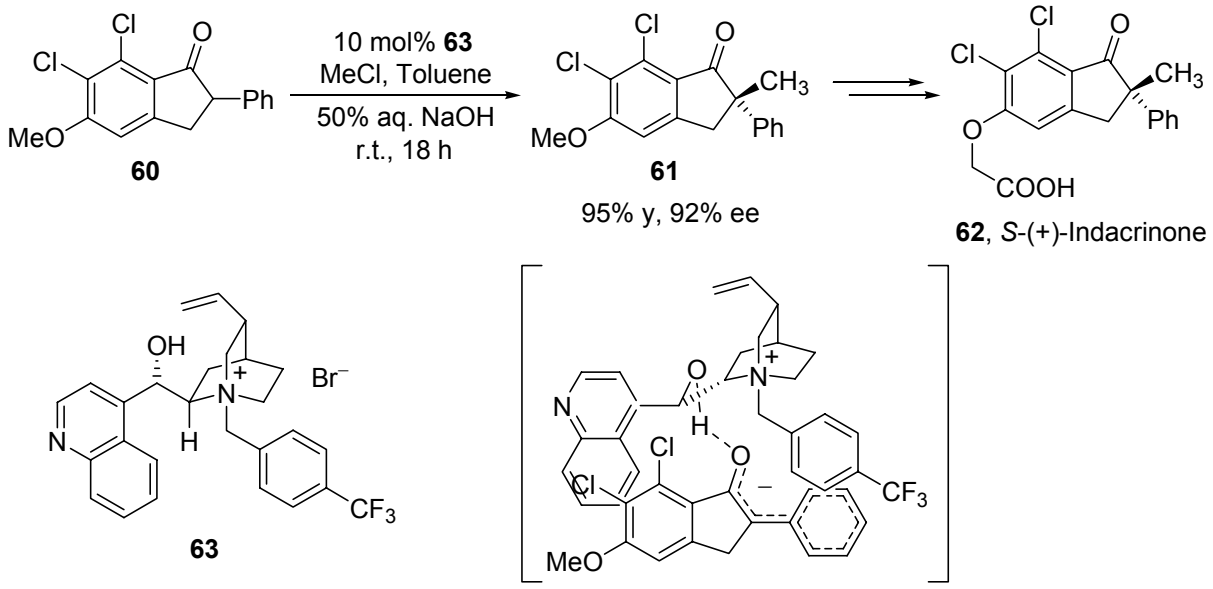
that *O*-alkylation and the bulkiness of the substituent at the quaternary quinuclidine nitrogen play crucial roles in the reaction stereoselectivity. This observation was immediately fructified and new *N*-benzyl-*O*-alkylated derivatives were subsequently synthesized (second generation of catalysts). A significant improvement in the selectivity was achieved by replacing the benzyl group of the quaternary ammonium ion with the bulkier anthracen-9-ylmethyl group (third generation of catalysts). The three generations of these catalysts are illustrated in the Scheme 19.



Scheme 19: Selected Cinchonidinium Quaternary Ammonium Salts Used in the PTC.

A breakthrough in the field was the enantioselective synthesis of the uricosuric agent **62**. The establishment of the stereogenic center in the methylindanone derivative *via* chiral PTC is the key step of the synthesis developed by the group of Dolling at Merk in 1984.[70] Enantiomeric excesses of up to 94% were achieved using *p*-trifluoromethylbenzylcinchoninium bromide **63** as catalyst.

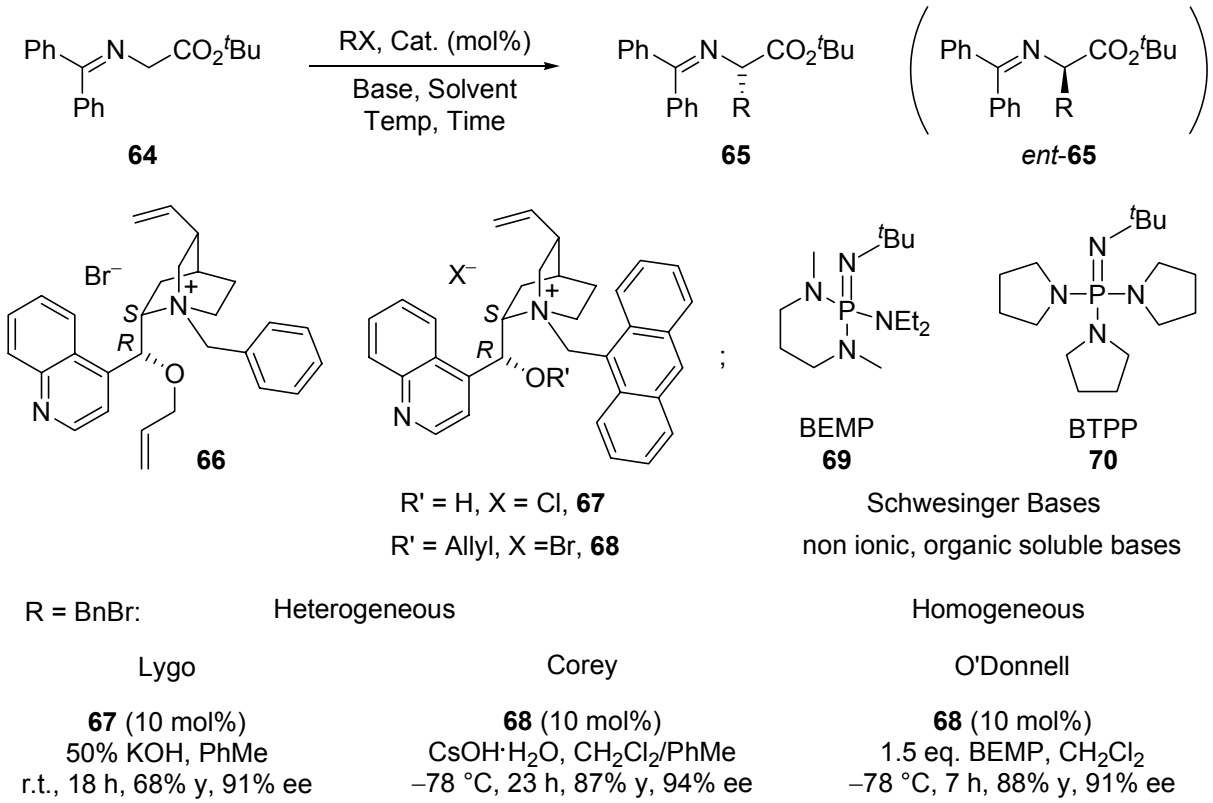
In the TS, the enolate substrate approaches the top face of the catalyst where it is positioned by hydrogen bonding effects and π-π stacking interactions between the aromatic rings of the catalyst and enolate. Subsequent methylation from the exposed face of the enolate yields the observed isomer (Scheme 20).



Scheme 20: Enantioselective Alkylation of Indanone under PTC.

A series of significant achievements in the field of alkylation followed the reaction described above. Both, racemic and optically active natural and unnatural α-amino acids have been synthesized by means of PTC. Achiral quaternary ammonium salts were employed in the synthesis of racemic mixtures. Enantioselective alkylation of glycine and alanine Schiff bases under PTC conditions, subsequent recrystallization (if required) and deprotection yields the corresponding free α-amino acids in optically pure form.[71] Benzophenone imines of glycine esters are suitable for small as well as for large scale preparation of the amino acids. The monoalkylation process can be easily controlled by using mild basic systems (NaOH, KOH, K_2CO_3). Only moderate levels of enantiocontrol (up to 66% ee) were achieved in this process using the first generation of *N*-benzyl cinchona salts developed by Dolling. The first improvement in the enantioselectivity was reported by O'Donnell.[72] In consideration of the fact that the active catalytic species in the alkylation process are formed *in situ* by *O*-alkylation of the cinchona quaternary ammonium salt, O'Donnell introduced pre-formed *N*,*O*-dialkylated cinchona salts **66**.[72c] Additional optimization of the reaction conditions led to significantly higher enantioselectivities (up to 81% ee). The next major improvement in the reaction selectivity was reported in 1997 by Lygo[73] and Corey[74] independently. Enantioselectivities of up to 99.5% were obtained by using a new

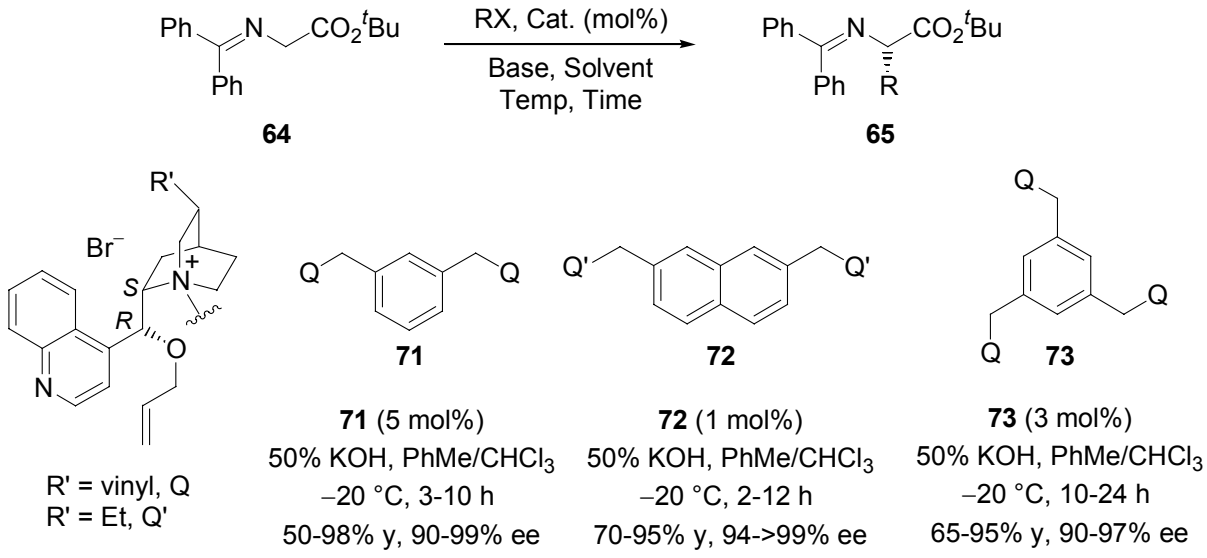
generation of catalysts bearing an anthracen-9-ylmethyl group with either a free OH or an *O*-alkyl group (Scheme 21).



Scheme 21: Enantioselective Alkylation of Glycine Imine.

More recently, Lygo has developed a new procedure, suitable for automated catalyst screening, involving *in situ* generation of the quaternary ammonium salt catalysts (*in situ N* and *O*-alkylation) during the liquid-liquid phase transfer alkylation process.[75] Application of this new protocol resulted in enantioselectivities comparable with those obtained by using pre-formed *N*,*O*-dialkylated catalysts. With the third generation of catalysts in hand, and by replacing the inorganic hydroxides with the non ionic, organic soluble bases **69** and **70**, O'Donnell and Schwesinger have developed a homogeneous version of the alkylation process which gives comparable results and considerably shorten the reaction time (Scheme 21).[76] In addition, a convenient procedure for the multigram synthesis of **68** has been developed by Corey.[77]

In search of better catalysts and taking into account the development of Sharpless' bis-cinchona alkaloids for the asymmetric dihydroxylation, new di- and trimeric cinchona alkaloid ammonium salts have next evolved. Two groups, Park[78] and Nájera,[79] have worked intensively on the design and synthesis of such types of cinchona derivatives. Several dimeric species with a spacer group between the cinchona units have been synthesized and evaluated in the enantioselective alkylation reaction. Among them, **71** and **72** led to a considerable increase in both enantioselectivity (90->99% ee) and scope of the substrate (active & nonactive alkyl halides performed excellently in the reaction). In addition the catalyst loading could be reduced even to 1 mol% in the case of naphthalene-based catalyst **72** without any decrease in the selectivity. Also the first total synthesis of (–)-antofine, a potent cancer cell growth inhibitor, could be now achieved by means of PTC.[80] The chirality was introduced into the molecule in an alkylation step which employs dimeric derivative **72** as catalyst. Similar dimeric-type catalysts have also been reported by Nájera. Unfortunately, the new dimeric species, with a bulkier 9,10-dimethylanthryl group between the cinchona moieties, could not compete with the catalysts developed by the group of Jew and Park.



Scheme 22: Selected di- and trimeric Cinchona Alkaloid Derivatives.

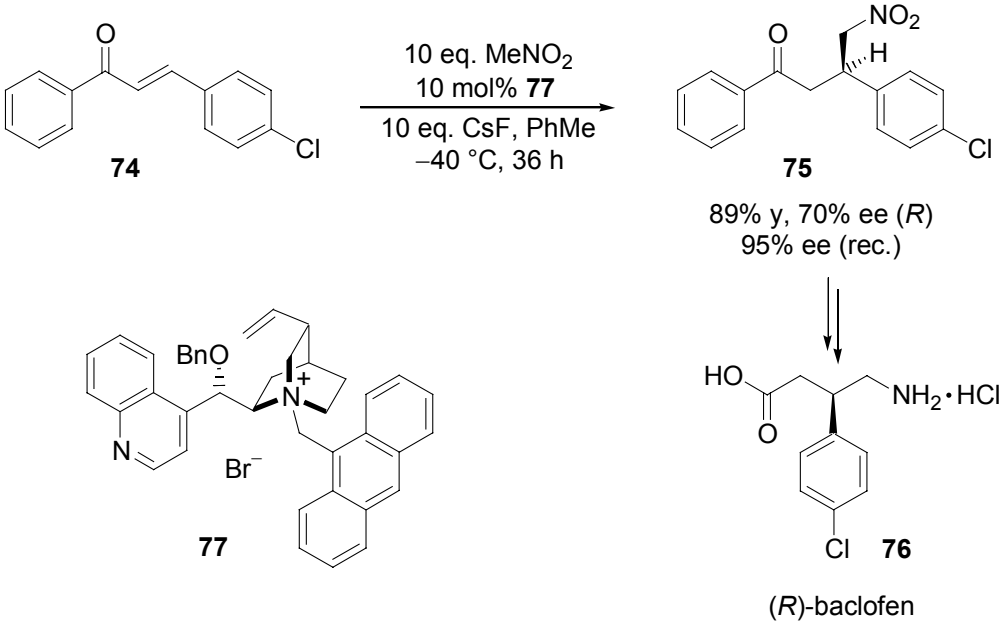
1.3.1.2 Aldol condensation

Since the PTC alkylation of glycine Schiff bases gave promising results, some cinchonine and cinchonidine derivatives were subsequently tested in the aldol and Michael reactions. The direct aldol reaction between glycine donors and aldehyde acceptors constitutes a convenient route to β-hydroxy-α-amino acids. Catalysts from the first generation exhibited modest levels of diastereo- and enantiocontrol in the aldol reaction between glycine derivative **64** and different aliphatic and aromatic aldehyde acceptors. A significant improvement in the enantioselectivity could be achieved by switching from the Schiff base **64** to the corresponding trimethylsilyl enol ether and from the first to the third catalyst generation.[81]

1.3.1.3 Michael addition

Recent reports from Corey have demonstrated that the third generation of catalysts is also highly efficient in the conjugate addition reactions.[82] Enantioselective Michael addition with glycine anion equivalents provides a convenient route to various functionalized α-alkylamino acids. Accordingly, naturally occurring (*S*)-glutamic acid (95% ee)[82a] and (*S*)-ornithine (91% ee)[82b] are readily available by means of chiral PTC when the Michael acceptors involved are methyl acrylate and acrylonitrile respectively. It is also worthy of note that if the same catalyst is used to promote both PTC enantioselective alkylation and addition reaction, the same major isomer (*S* or *R*) will be isolated. In both cases, the same enolate-catalyst combination is responsible for the high selectivity and the sense of asymmetric induction. The tight, structured ion pair between the ammonium cation and the enolate blocks one face (*re*) of the nucleophilic carbon center in the enolate and leaves only the other (*si* face) free for attack by the alkylating or electrophilic agent. The same methodology was recently applied in the synthesis of therapeutically useful $GABA_B$ receptor agonist (*R*)-baclofen.[83] The enantioselective Michael addition of nitromethane to the chalcone-derived enone **74** in the presence of cinchoninium salt **77** and powdered cesium fluoride afforded the product **75** in 89% yield and 70% ee. A single

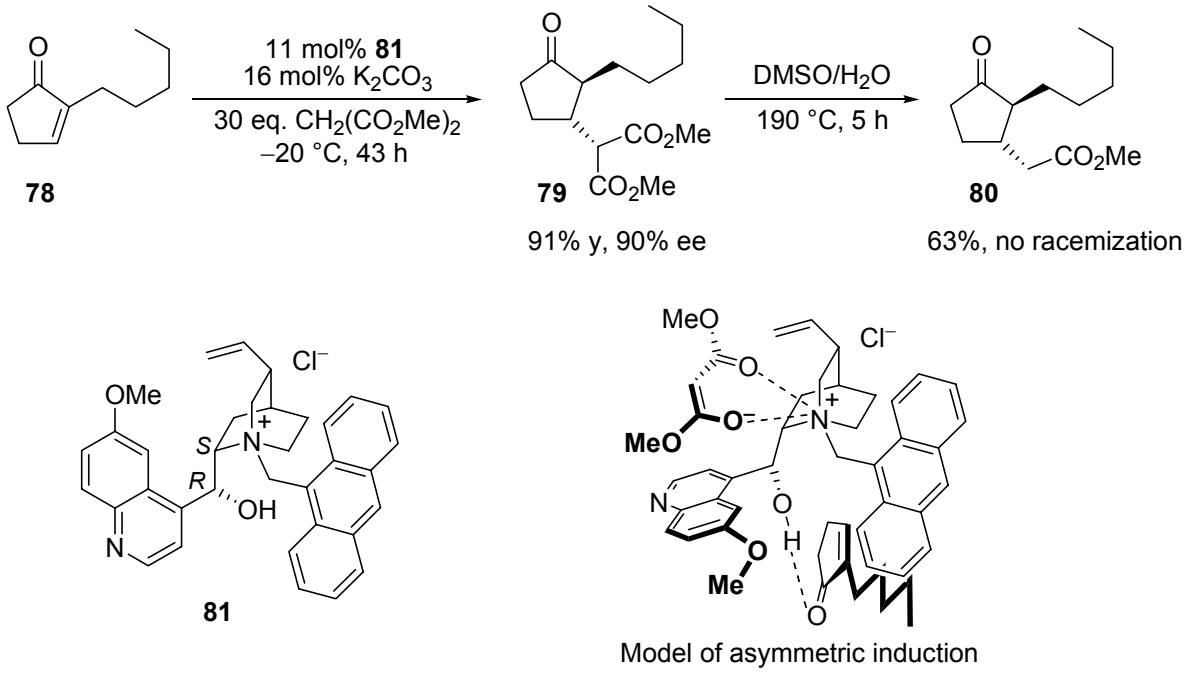
recrystallization allowed the ee to be increased to 95%. Subsequent Baeyer-Villiger oxidation, reduction and acidic hydrolysis afforded the desired product (*R*)-baclofen as its hydrochloric salt. The opposite enantiomer has been synthesized enantioselectively (95% ee) starting from the same precursor just by appropriate selection of the catalyst.



Scheme 23: Enantioselective Synthesis of (*R*)-Baclofen.

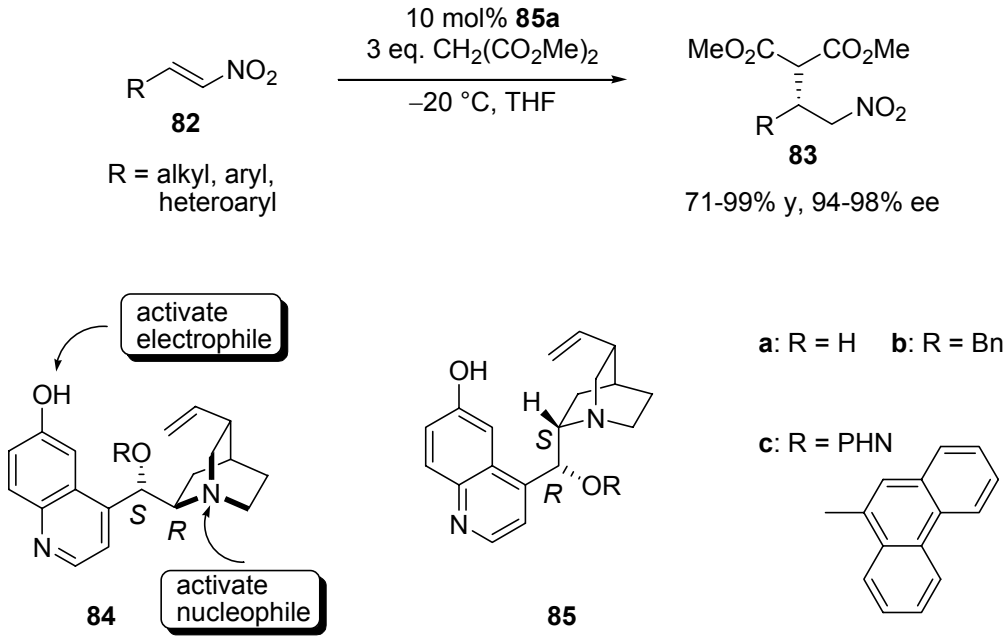
Plaquevent applied the PTC asymmetric Michael addition, as a key step, in the synthesis of both enantiomers of methyl dihydrojasmonate, important perfumery ingredients (jasmine-like odor).[84] Solvent free, solid-liquid phase transfer asymmetric addition of dimethylmalonate to enone **78**, catalyzed by cinchonidinium salt **81**, afforded **79** in 91% yield and 90% ee. Subsequent demethoxycarboxylation under Krapcho conditions yielded the desired product in good overall yield (Scheme 24).

A general protocol for the synthesis of optically active 1,5-diketones was next developed. Michael addition of trimethylsilyl enol ethers to α,β-unsaturated ketones under PTC conditions afforded the corresponding adducts in high yields (79-94%) and excellent enantioselectivities (91-95% ee).[85] Further advantages of the enol ethers over ketones as reactants are shorter reaction time and minimalization of the aldol side reaction.



Scheme 24: Synthesis of (+)-Methyl Dihydroiasmonate.

Recent contributions from Deng have shown that slight modification of the natural cinchona alkaloids provides remarkable catalysts for the asymmetric conjugate addition reaction. For example, quinidine and quinine derivatives **84** and **85**, in which the methoxy group has been replaced by a hydroxyl group, are highly effective in the addition of dimethylmalonate to nitroalkenes.[86] Moreover, the reaction proved to be quite general with respect to β-substitution on the nitroalkene electrophile. A large range of substituents including alkyl, heteroaryl, electron rich as well as electron deficient aromatic groups were tolerated during this process. Treatment of nitroalkenes **82** with dimethylmalonate in the presence of **85a** in THF at –20 °C afforded the corresponding 1,4-addition products in very high yields (71-99%) and with excellent enantioselectivities (94-98% ee). The opposite enantiomer was produced with slightly lower enantiomeric excess (91-96% ee) when the reaction was promoted by **84a**. In both cases, lowering the temperature to –55 °C had a positive effect on the asymmetric induction but required a three times longer reaction time.

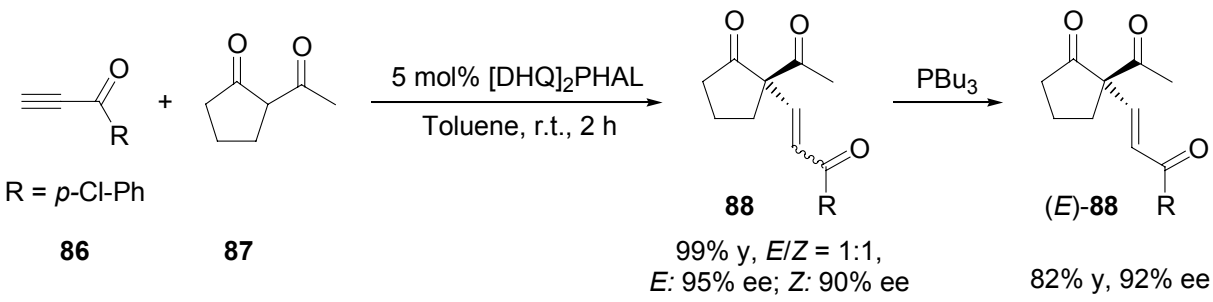


Scheme 25: 1,4-Addition of Dimethyl Malonate to Nitroalkenes.

The conjugate addition of a prochiral, trisubstituted carbon nucleophile to a prochiral β-substituted Michael acceptor is an efficient synthetic strategy because it allows the simultaneous formation of two vicinal stereogenic centers in a molecule. If the formation of the chiral centers could be diastereo- and enantioselectively controlled, this process would provide access to multifunctional compounds, useful building blocks in organic synthesis. Exceptional levels of asymmetric induction have been attained for various substrates with the cinchona alkaloid derived catalysts **84** and **85**.[87] As in the previously described example, a wide range of nitroalkene-electrophiles bearing alkyl, aryl or heteroaryl groups were found to be effective reaction partners in the conjugate addition. Diastereoselectivities ranging from 91:9 to (≥98):(≤2) and excellent enantioselectivities (99->99% ee) were obtained with various cyclic and acyclic β-ketoesters. Aprotic solvents (THF, ether, toluene) and lower temperature led to increased stereoselectivity. The methodology could also be applied to 1,3-diketones, cyanoacetate and nitro ester derivatives as Michael donors, yielding products with high diastereo- and enantiomeric excesses.

Jørgensen has developed a useful protocol for the organocatalytic enantioselective conjugate addition of β-dicarbonyl compounds to alkynones.[88] From a class of eight

selected catalysts, only Sharpless biscinchona alkaloid $[DHQ]_2PHAL$ gave promising results in the addition of acetyl cyclopentanone with butyn-2-one, affording the product as a 2:1 mixture of (*E*) and (*Z*) isomers with 70 and 40% ee respectively. The products are stable and may be separated by chromatography. A considerable increase in the enantioselectivity (up to 95% ee) was observed when aromatic alkynones were employed as substrates (Scheme 26). In addition, the isomerization of the (*Z*)-isomer to the more stable (*E*)-isomer could be accomplished in the same step, using a catalytic amount of Bu_3P, without affecting the yield or the enantioselectivity. Moreover, the newly developed protocol is of synthetic utility because the presence of a carbon-carbon double bond next to the carbonyl groups allows further functionalization.

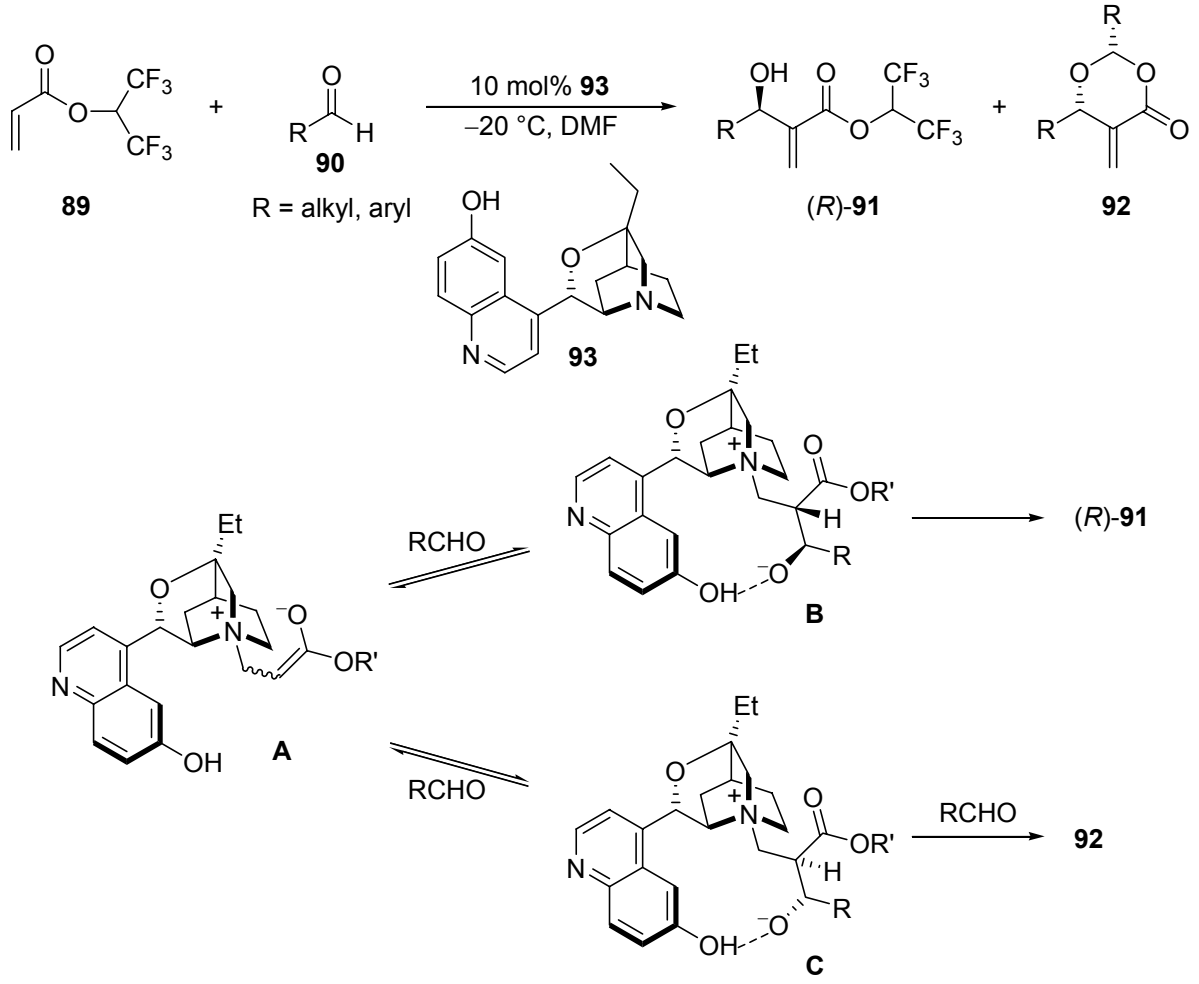


Scheme 26: Organocatalytic Enantioselective Conjugate Addition to Alkynones.

1.3.1.4 Baylis-Hillman reactions

The base catalyzed reaction of aldehydes with activated alkenes, such as acrylates, provides a convenient route to α-methylene-β-hydroxycarbonyl compounds, which are useful precursors in the synthesis of natural products and biologically active substances. Within the last few years, several research groups have focused their attention on the development of an efficient, asymmetric version. In principle, this could be achieved either by using chiral substrates (chiral activated alkenes or chiral electrophiles) or by employing chiral catalysts. Despite all efforts, only unsatisfactory results (low conversion and low asymmetric induction) were obtained when brucin, *N*-methylprolinol, *N*-methylephedrine, quinidine and nicotine were employed as chiral

base catalysts.[89] The first significant improvement was reported by Leahy in 1997 and employs the use of Oppolzer sultame as chiral auxiliary in DABCO-catalyzed Baylis-Hillman reactions.[90] Soon after, the first highly enantioselective catalytic version was described by Hatakeyama.[91]

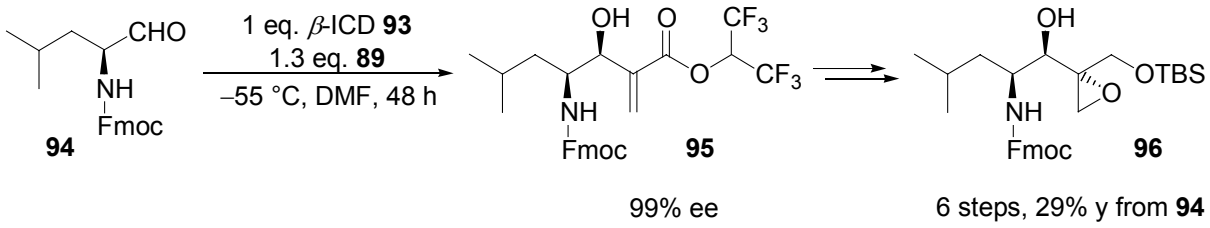


Scheme 27: Asymmetric Baylis-Hillman Reaction.

A large variety of aromatic and aliphatic aldehydes were reacted with hexafluoroisopropyl acrylate (HFIPA) (**89**) in the presence of 10 mol% β-isocupreidine (β-ICD) (**93**) as chiral amine catalyst, to give products in 31-51% yield and 91-99% ee (Scheme 27). The rigid tricyclic quinidine-derived chiral amine β-ICD (**93**), DMF and low temperature were found to be optimal for an enantioselective reaction. The increased nucleophilicity of the β-ICD compared to quinidine, the *anti-open* alkaloid conformation and the presence of the free hydroxyl group on the

quinoline moiety seems to be responsible for the asymmetric induction. Conjugate addition of the amine to the acrylate yields the enolate **A**. Attack on the aldehyde **90** by the enolate **A** generates two diastereomeric intermediates **B** and **C**, stabilized through intramolecular hydrogen bonding. While betaine **B** possesses the required conformation for the elimination reaction (yielding the product), betaine **C** suffers from severe steric interactions and therefore undergoes reaction with a second aldehyde molecule, affording the dioxanone **92**. Formation of the dioxanone byproducts, which considerably decreases the yield of the desired product, constitutes one drawback of Hatakeyama's protocol.

Despite low yield, the synthetic utility of this methodology has been demonstrated in the synthesis of (–)-mycestericin E,[92] a potent immunosupressor, and epopromycine B,[93] an inhibitor of cell wall synthesis in plants. The synthesis of the key precursor of epopromycin B is illustrated in Scheme 28.

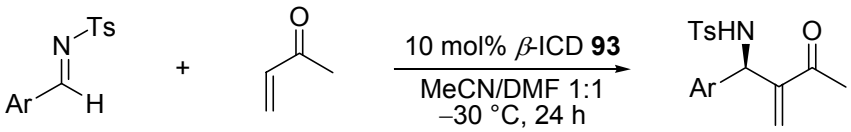


Scheme 28: Application of the Asymmetric Baylis-Hillman Reaction in the Synthesis of Epopromycin B.

Nowadays, intensive research is also being carried out for the improvement of the related aza-Baylis-Hillman reaction. Reported for over twenty years ago, the reaction between methyl acrylate and preformed imines offers an attractive alternative route to α-methylene-β-amino acid derivatives.[94] The achiral version of the reaction has been well documented by the group of Shi.[95] Making use of their vast experience in the field, and the findings of Hatakeyama, Shi investigated and developed a metal-free catalytic asymmetric version.[96]

Several aromatic *N*-tosylated imines were evaluated in the reaction with methyl-vinyl ketone (MVK) (**98**) in the presence of 10 mol% β-ICD (**93**). In the preliminary investigations, the best ee values were observed at –30 °C in DMF, and the best

yields were obtained at −30 °C in MeCN. Thus, different DMF/MeCN solvent combinations were tested, and the best results were obtained in a 1:1 mixture. With one exception (Ar = C_6H_5CHCH-), various aromatic *N*-tosylated imines **97** were reacted with MVK (**98**) to give (*R*) configured products **99** in good yields (55-80%) and with high ee's (73-99%) (Scheme 29).[96] Methyl acrylate, as donor, required a longer reaction time and gave products with opposite absolute configuration in comparable yields (58-87%) although slightly lower ee values ((*S*), 70-83%).[96b] Any attempts toward extending the reaction scope to aliphatic *N*-tosylated imines failed due to their high instability, even when stored at low temperature.

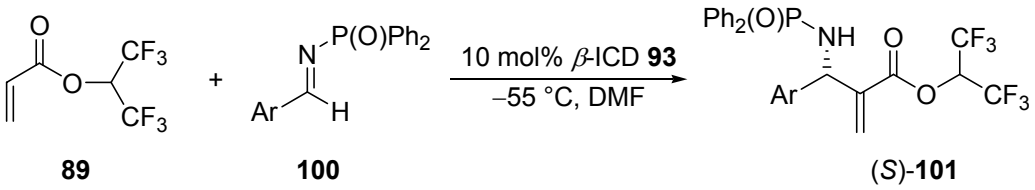


97 **98** (*R*)-**99**

Scheme 29: Asymmetric aza-Baylis-Hillman Reaction According to Shi.

A one-pot three-component aza-Baylis-Hillman reaction between acrylates, aldehydes and tosylamines has been reported by Adolfsson.[97] A combination of an achiral Lewis acid with a chiral Lewis base and 4Å molecular sieves additives are responsible for the increased yield and selectivity. Accordingly, various aromatic aldehydes were reacted at r.t. in THF with tosylamines and methyl acrylate, in the presence of 15 mol% β-ICD (**93**) and 2 mol% titanium isopropoxide, to give aza adducts in high yields (78-95%) and moderate enantioselectivities ((*R*), 49-74% ee).

In his recent studies on the aza-Baylis-Hillman reaction, Hatakeyama[98] showed that β-ICD (**93**) promoted reaction between various *N*-protected aromatic imines and HFIPA proceeds with (*S*)-selectivity. Due to the ease of their deprotection, *N*-diphenylphosphinoyl aromatic imines **100** were chosen for further investigations (Scheme 30). Since the products were crystalline, the moderate enantioselectivities (54-73% ee) observed in the reaction could be increased by simple recrystallization ((*S*), 93-100% ee).



89 **100** (*S*)-**101**

Scheme 30: Asymmetric aza-Baylis-Hillman Reaction According to Hatakeyama.

Although great progress has been made in view of asymmetric induction, the Baylis-Hillman reaction still suffers from slow rate, low yield and limited substrate scope. Concerning the reaction rate, additional information was furnished by Aggarwal who found a direct correlation between the catalyst basicity and its reactivity: the higher the pK_a value, the faster the reaction.[99]

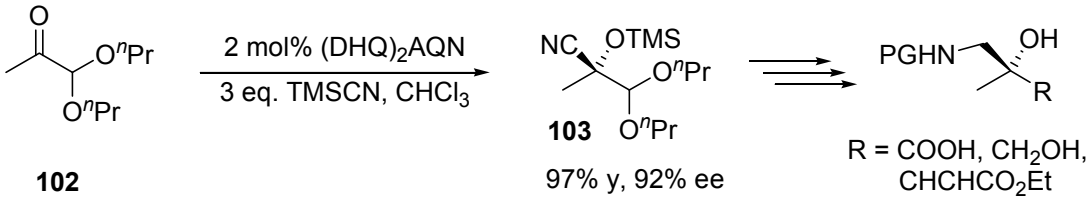
1.3.1.5 Asymmetric cyanation of ketones

As already mentioned, the enantioselective hydrocyanation of aldehydes and imines is a versatile synthetic transformation, providing important synthons for organic synthesis. Conversely, the asymmetric cyanation of ketones is still considered as problematic.[49] The first reports in this area employed chiral metal-based Lewis acids as catalysts and were dominated by low yields and selectivities. The first general protocol was reported by Shibasaki.[100] Titanium and gadolinium based complexes were found to effectively catalyze the addition of TMSCN to prochiral ketones.

In 2001, Deng reported the first Lewis base catalyzed cyanation of ketones.[101] Addition of ethyl cyanoformate to structurally diverse ketones proceeded with high selectivity when modified cinchona alkaloids were employed as catalysts. With one exception, 2-heptanone, the 1,2-addition was highly selective (81-97% ee) for a large range of cyclic and acyclic sterically hindered dialkylketones. The reaction is claimed to proceed cleanly, although, for several substrates a strong discrepancy exists between the reported yield, conversion into the product and conversion from ketone.

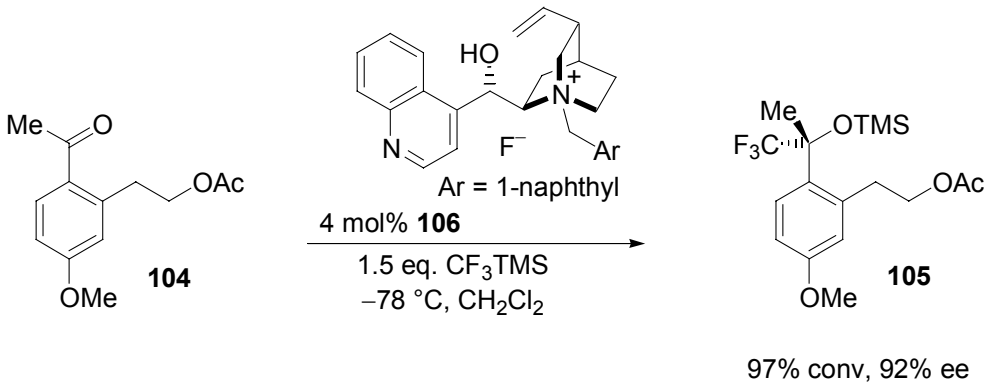
As an extension of this field, cyanosilylation of ketones with modified cinchona alkaloids was next investigated.[102] While simple ketones afforded products with low to moderate enantioselectivity, acetal ketones proved to be effective substrates. A

broad range of acetal ketones, bearing aryl, alkenyl, alkynyl and alkyl substituents were reacted with TMSCN to give products in good to excellent yields (81-99%) and with high selectivities (90-98% ee). The reaction has found synthetic applications in the synthesis of enantiomerically enriched amino alcohols, hydroxy amino acids and their derivatives (Scheme 31).



Scheme 31: Catalytic Asymmetric Cyanosilylation of Acetal Ketones.

Caron has developed a highly specialized cinchonine derived catalyst for the enantioselective addition of a trifluoromethyl anion to aryl ketone **104**.[103] Activation of Ruppert's reagent CF_3TMS by the fluoride counterion of the catalyst enabled the trifluoromethyl anion formation. Under optimized conditions (4 mol% cat, −78 °C, CH_2Cl_2), the product could be isolated with 92% ee. Unfortunately the catalyst is not generally applicable to other ketone and aldehyde substrates. Attempts to extend the substrate scope resulted in high conversion but disappointing enantioselectivities.

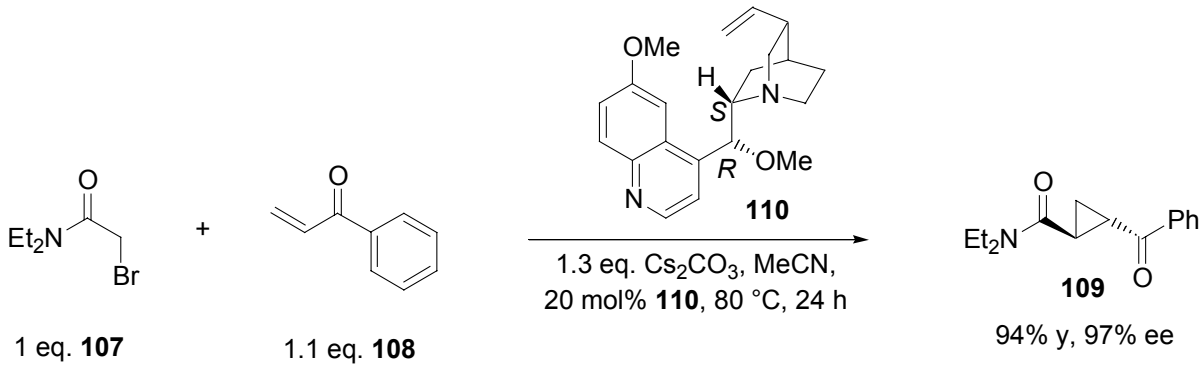


Scheme 32: Enantioselective Nucleophilic Addition of CF_3TMS to Ketones.

1.3.1.6 Cyclopropanation

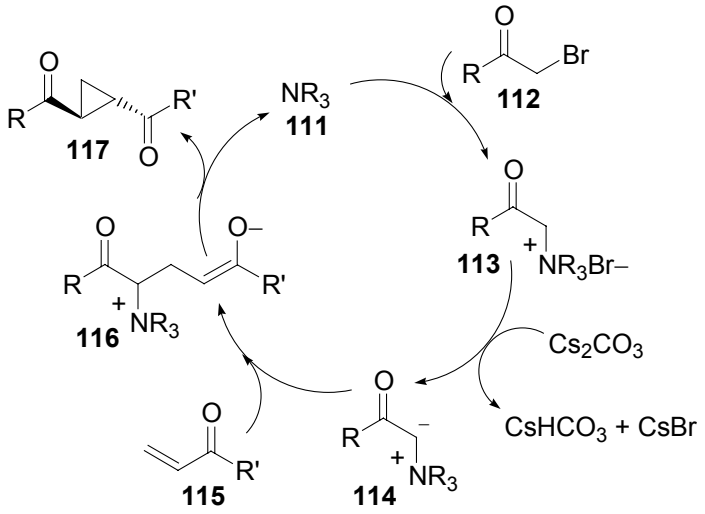
The cyclopropane unit is a key structural element in a wide range of synthetic as well as naturally occurring biologically active substances. Therefore, much effort has been made toward their diastereo- and enantioselective synthesis. Significant advances have been registered in the field of both Simmons-Smith type cyclopropanation and metallocarbenoid chemistry.[104] As an alternative, cinchona alkaloid mediated asymmetric cyclopropanation[105] *via* ammonium ylides has recently gained considerable attention. The initial studies dealt with the elaboration of a general diastereoselective reaction protocol amenable to the [2+1] inter- and intramolecular versions. While catalytic amounts of the achiral tertiary amine were employed in the intramolecular version, stoichiometric amounts were required for the intermolecular reaction.

Use of cinchona alkaloids resulted in a highly diastereo- and enantioselective reaction applicable to a large range of substrates. For example, the *trans* product was isolated as a single diastereomer in high yield (60-96%) and enantioselectivity (80-97% ee) by the intermolecular reaction of different α-bromo carbonyl compounds with various enones and acrylates (Scheme 33). It is notable that this strategy avoids the use of highly sensitive diazo compounds and the reaction therefore constitutes another great achievement in the field of organocatalysis.



Scheme 33: Enantioselective Organocatalytic Cyclopropanation.

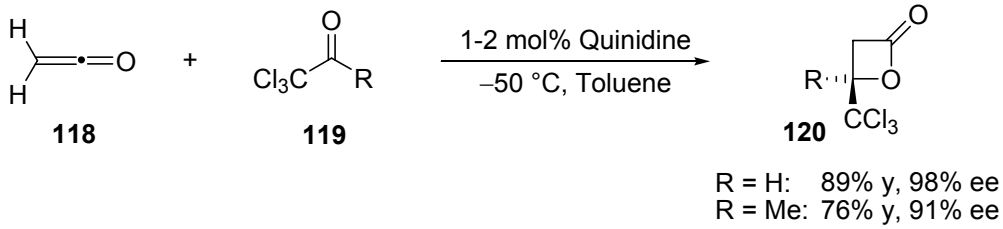
Concerning the reaction mechanism, it is assumed that the bromo carbonyl compound **112** reacts with the tertiary amine **111** yielding a quaternary ammonium salt **113**. Deprotonation by cesium carbonate forms the ylide **114** which undergoes conjugate addition to enone **115** to form **116**. Subsequent 3-*exo*-*tet* cyclization affords the cyclopropane **117** and regenerates the catalyst **111**.



Scheme 34: Proposed Catalytic Cycle for the Cyclopropanation Reaction.

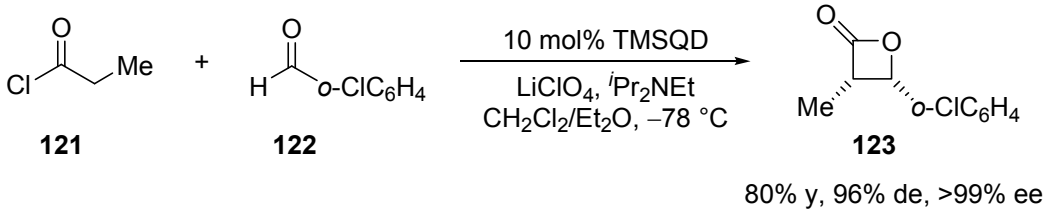
1.3.1.7 [2+2] Cycloaddition reactions

In the early 1980's, Wynberg[106] reported excellent asymmetric induction in the cinchona alkaloid catalyzed [2+2] cycloaddition between highly activated carbonyl compounds, such as chloral **119** (R = H), and ketene **118** (Scheme 35).[107] Nucleophilic addition of the alkaloid to the ketene yields an acylammonium enolate which undergoes addition to aldehyde, generating a new zwitterionic intermediate. Subsequent cyclization affords the β-lactone and regenerates the chiral amine catalyst. Both enantiomers of the lactone are readily available with up to 98% ee by employing 1-2 mol% of the pseudoenantiomeric **QD**-**QN** alkaloids as catalyst.



Scheme 35: β-Lactone Synthesis According to Wynberg.

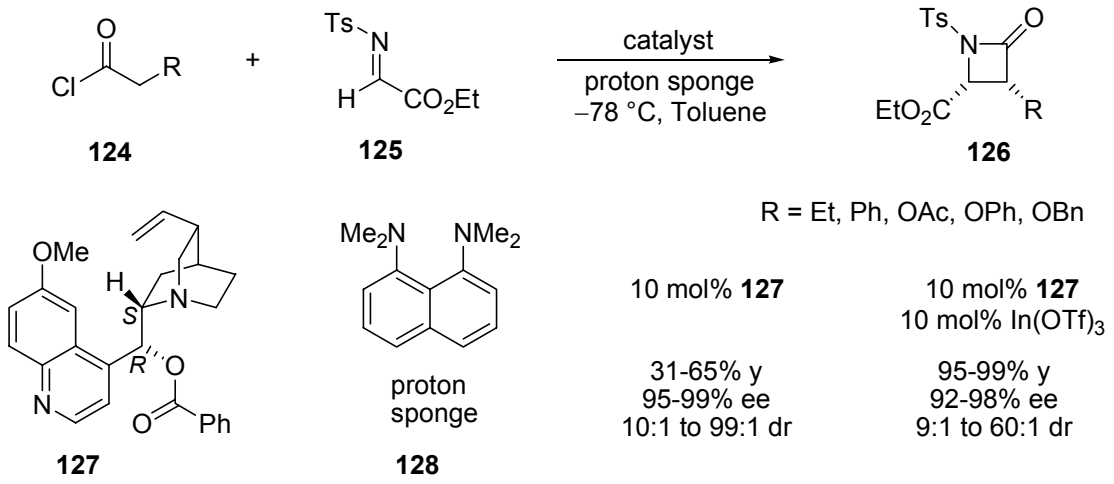
Although the method is efficient and has been commercialized for the large-scale production of optically pure malic and citramalic acids, there are some limitations concerning the nature of the electrophile and the ketene generator. Recent reports by Romo[108] and Nelson[109] describe solutions to these problems. *In situ* generation of the ketene[107] by dehydrohalogenation of acid chlorides with Hünig's base resulted in high yields (40-85%) and selectivities (93-98% ee) which are comparable with those obtained by using preformed ketenes. As in the previous case, the reaction only proceeded with highly electrophilic carbonyl compounds (α-di- and trichlorinated ones).[108] It has been hypothesized that Lewis acid activation of the electrophile substrate would offer an alternative method for the use of non-activated aldehydes. For this purpose, a bifunctional catalytic system consisting of a chiral Lewis base/achiral Lewis acid cocatalyst was investigated. Diisopropylethyl amine (2.5 eq.) was employed for the *in situ* ketene generation. A combination of *O*-trimethylsilyl quinidine and lithium perchlorate emerged as an effective catalyst/cocatalyst system. For the first time, structurally diverse aldehydes were reacted with methylketene to give β-lactones in high yields (70-85%) and with excellent enantioselectivities (84-96% ee). An exceptional level of asymmetric induction was also observed when propionyl chloride-derived methylketene was employed in the reaction. In all cases *cis*-substituted β-lactones were isolated as major diastereomers (mostly >90% de) with up to >99% ee.[109]



Scheme 36: β-Lactone Synthesis According to Nelson.

Calter reported the cinchona alkaloid catalyzed dimerization of methylketene, generated *in situ* either from α-bromopropionyl bromide[110] or by thermolysis of propionic anhydride.[111] Trapping of the ketene dimer with a secondary amine and subsequent aldol reaction provides convenient access to complex polypropionate systems.[112] In this manner, ketene dimerization served as a synthetic tool in the asymmetric synthesis of $C_{1'}$-$C_{10'}$ segment of the macrocyclic antibiotic pamamycin 621A.[113]

Although the reaction between ketene and imines proceeds at low temperature without catalyst, and usually chiral auxiliaries are required in order to effectively control the stereochemistry of β-lactam formation, Lectka's recent studies have shown that nucleophilic catalysis can also provide excellent levels of asymmetric induction.[114] It has been demonstrated that benzoylquinine in combination with a non-nucleophilic amine base, such as proton sponge, catalyzes the addition of various ketenes (R = Et, vinyl, Ph, OAc, OPh, OBn) to tosyl imine, yielding the *cis* β-lactams (99:1 dr) in moderate yield (45-65%) and with high enantiomeric excesses (95-99% ee).[115] A significant decrease in the diastereoselectivity (98:2 to 10:1 dr) was registered when the substituent on the acid chloride was R = F, Br, N_3, CH_2OPh or 2-Np, but the reaction was still highly enantioselective (95-97.5% ee).[116] Regarding the mechanism, it is assumed that free ketenes are not involved in the reaction, and that the acid chloride reacts with benzoylquinine to form, in a first step, an acylammonium salt intermediate. Subsequent deprotonation by the proton sponge yields a zwitterionic enolate which then reacts with the imine to give the β-lactam. The enolate formation is accomplished by the formation of 1 eq. of proton sponge hydrochloride which precipitates from the reaction solution.



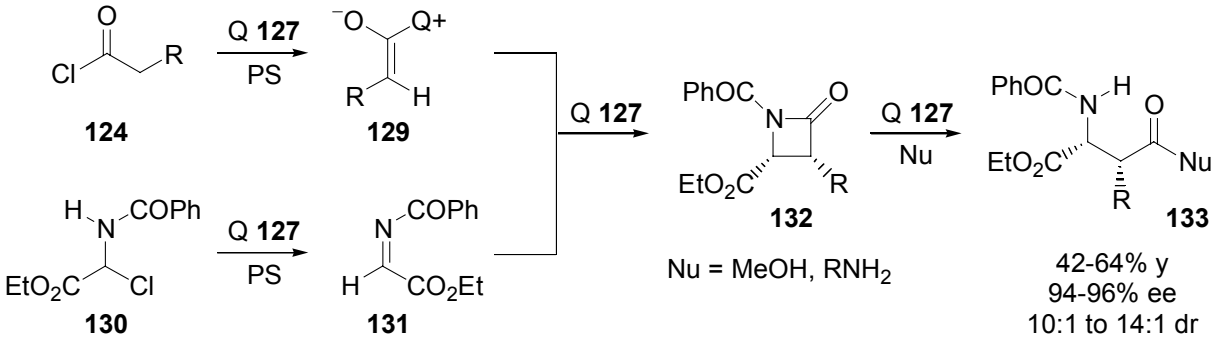
124 **125** **126**

127 **128**

Scheme 37: β-Lactam Synthesis According to Lectka.

On the basis that Lewis acid activation of the imine would favor the desired cycloaddition pathway, suppressing the possible side reactions and thus increasing the yield, a combination of Lewis acid and Lewis base was next investigated.[117] It was found that addition of 10 mol% $In(OTf)_3$ to the reaction mixture increased the yield considerably (95-99%) without lowering the enantioselectivity (92-98% ee); the diastereoselectivity, however, was affected (Scheme 37).

Next, a general multistage, one-pot procedure for the synthesis of β-substituted amino acids was elaborated (Scheme 38).[118] Due to its easy removal, the tosyl group was replaced by a benzoyl protecting group. It is notable that the cinchona alkaloid catalyst plays four distinct roles during the synthesis: (1) catalytic dehydrohalogenation of the acid chloride to generate the enol **129**; (2) dehydrohalogenation of the *N*-acyl-α-chloroamine to form the corresponding imine **131**; (3) catalysis of the [2+2] cycloaddition to afford the β-lactam **132** and (4) catalysis of the nucleophilic ring opening of the lactam to yield optically enriched β-substituted amino acid derivatives **133**.



Scheme 38: One-pot Multicomponent β-Substituted Amino Acids Synthesis.

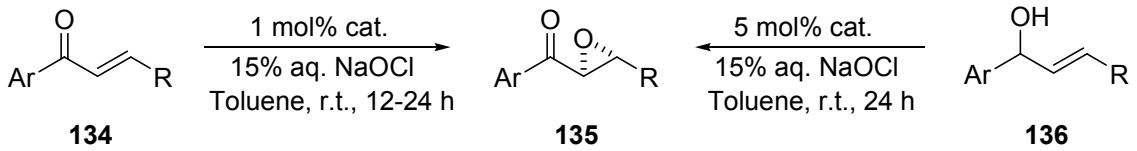
The *in situ* ketene generation was successfully extended to the catalytic, asymmetric α-halogenation of acid chlorides.[119] Once formed, the zwitterionic enolate intermediate is attacked at the α-position by the electrophilic halogenating reagent yielding an acylammonium salt. Transacylation with the leaving group of the electrophile leads to the α-halogenated products, liberating also the catalyst. Accordingly, α-chloro[119a,b] and α-bromo esters[119c] are easily available with up to 81% yield and 99% ee.

1.3.2 Carbon-oxygen bond formation

1.3.2.1 Epoxidation

As already mentioned in chapter 1.2.2, Juliá-Colonna epoxidation impose on as an efficient synthetic method for the enantioselective functionalization of α,β-unsaturated enones. More recently, the asymmetric epoxidation of electron deficient olefins by means of PTC emerged as an alternative method. Wynberg reported for the first time in 1976, the use of a chiral phase catalyst in a biphasic Weinz-Scheffer asymmetric epoxidation.[120] Modest levels of asymmetric induction (up to 54% ee) were attained when catalytic amounts of simple *N*-benzyl salts of cinchona alkaloids were employed in the reaction.[121] Twenty years later, Taylor achieved an enhancement in the enantioselectivity (89% ee, 99.5% ee after two recrystallizations) by using a

stoichiometric amount of cinchona alkaloid derivative, TBHP in toluene and a catalytic amount of sodium hydroxide.[122] In light of the excellent results obtained with the third generation of catalysts in the asymmetric alkylation reaction, Lygo[123] and Corey[124] independently examined their utility in the PTC oxidation of enones. Lygo's detailed studies led to the development of an improved protocol for the epoxidation reaction. A wide range of substituted chalcones and alkyl substituted enones were selectively oxidized (≥95% de, 69-90% ee) in the presence of sodium hypochloride as stoichiometric oxidant and 10 mol% catalyst. In addition, a more efficient protocol for the chalcone epoxidation has been disclosed. A decrease to 1 mol% in the catalyst loading did not alter the reaction selectivity and the *trans* epoxides were isolated with up to 92% ee (≥98% ee after recrystallization) (Scheme 39). Interestingly, the direct conversion of secondary allylic alcohols into enantiomerically enriched α,β-epoxyketones could be achieved under the same reaction conditions (Scheme 39).[125]



134 **135** **136**

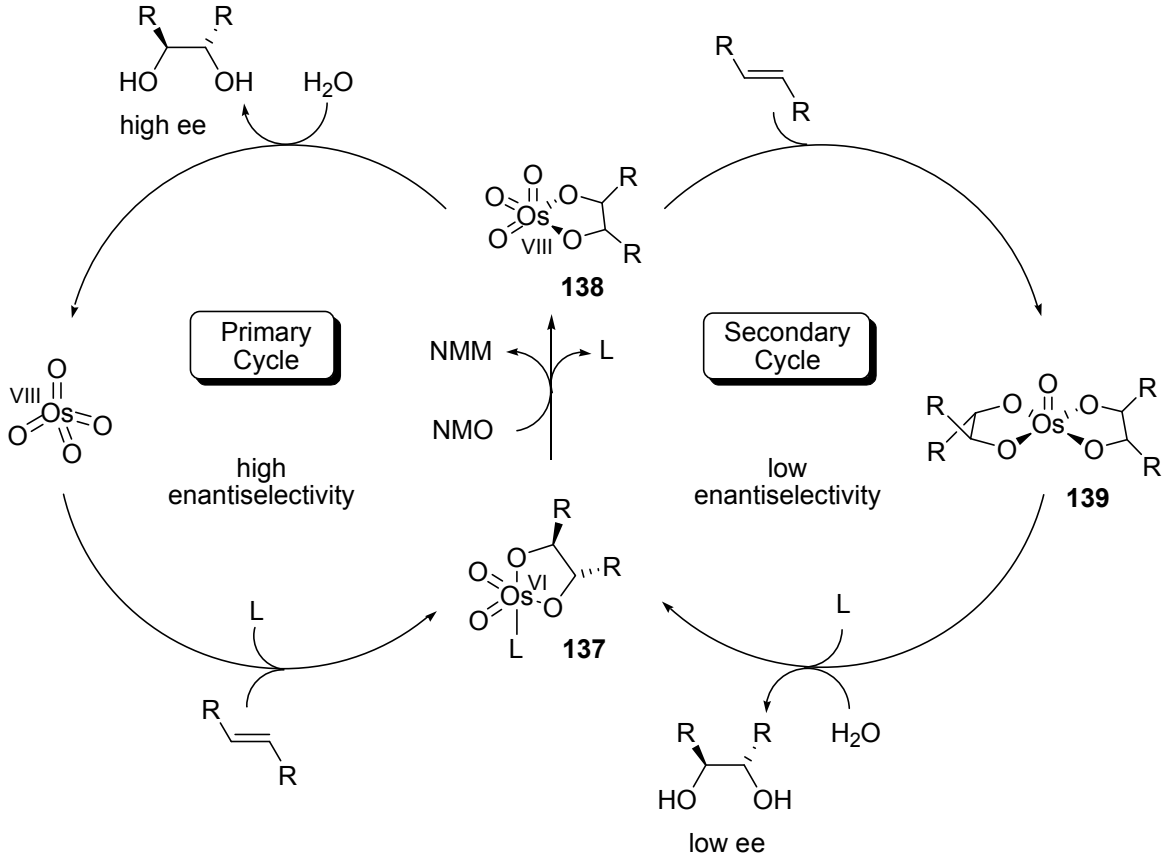
Scheme 39: Asymmetric Epoxidation *via* Phase-Transfer Catalysis.

Corey developed a similar protocol for the epoxidation of enones which gives slightly higher enantiomeric excesses (91-99% ee).[124] Shioiri designed new phase transfer catalysts[126] but they were less effective in the epoxidation reaction.

1.3.2.2 Asymmetric dihydroxylation

Asymmetric dihydroxylation is one of the most powerful catalytic asymmetric reactions which has been developed in the last twenty years. An enormous contribution to this field came from Sharpless who was awarded with the Nobel Prize in 2001. The initial asymmetric dihydroxylation process was stoichiometric in both chiral ligand and expensive OsO_4 as oxidizing reagent.[127] Moderate to good

enantiomeric excesses were obtained when stoichiometric amounts of acetate esters of cinchona alkaloids were employed as chiral ligands in the osmylation reaction.
The first catalytic version was based on the *Upjohn* process and made use of *N*-methylmorpholine-*N*-oxide as stoichiometric reoxidant.[128] Unfortunately, the enantioselectivities obtained in the catalytic version were slightly lower compared to those obtained under stoichiometric conditions. Mechanistic studies revealed that the origin of this discrepancy lies in the presence of a second, non-selective catalytic cycle (Scheme 40).[129]

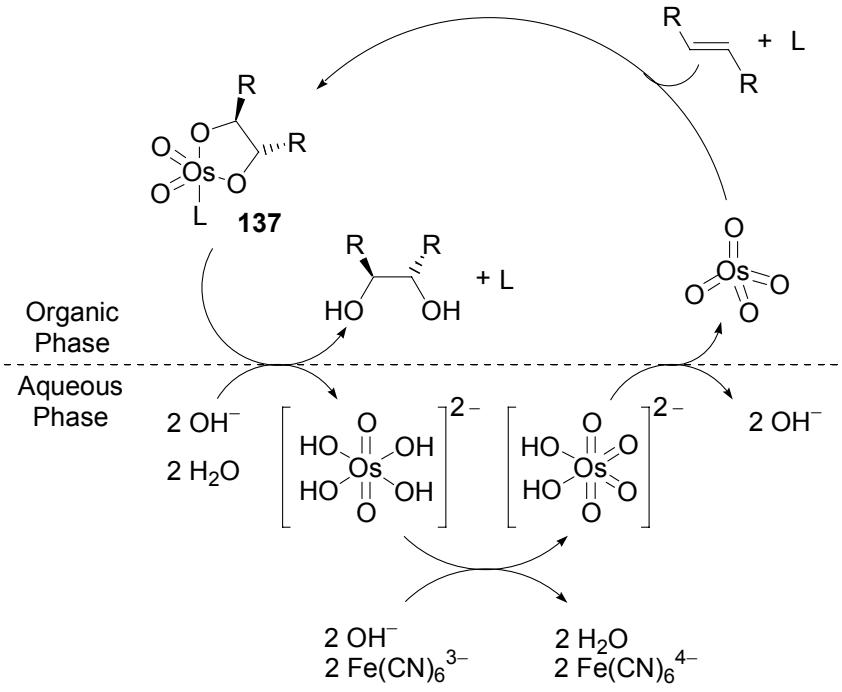


Scheme 40: Proposed Catalytic Cycle for the AD using NMO as Cooxidant.

As depicted in Scheme 40, the primary catalytic cycle proceeds with high facial selectivity since it involves a chiral ligand in its selectivity-determining step, which is the formation of the osmium (VI) glycolate **137**. Subsequent oxidation by the NMO cooxidant results in the formation of osmium (VIII) glycolate **138** with concomitant loss of the chiral ligand. At this point the desired reaction pathway involves the hydrolysis of **138** to the enantiomerically enriched 1,2-diol with the formation of OsO_4.

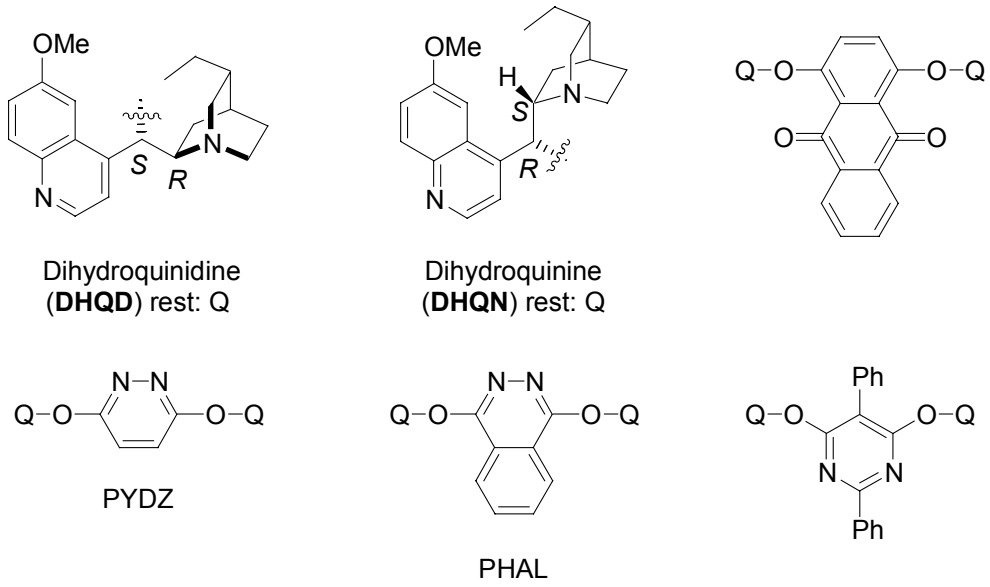
The undesired pathway appears when, instead of hydrolysis, **138** undergoes addition with a second olefin molecule, yielding the osmium (VI) bisglycolate **139** which upon hydrolysis liberates the product with low enantiomeric excess. However the problem could be circumvented by slow addition of the olefin.[129]

Several improvements followed, and now almost all classes of olefins can be dihydroxylated with excellent enantioselectivity.[130] The first considerable improvement in the catalytic version was the development of a two phase reaction system with $K_3Fe(CN)_6$ as stoichiometric inorganic cooxidant and a *tert*-butanol/water mixture as heterogeneous solvent system.[131] Under these conditions the osmylation takes place in the organic phase yielding the osmium (VI) glycolate **137** which upon hydrolysis liberates the diol and the ligand into the organic layer and the Os(VI) species into the aqueous layer where it is reoxidized to OsO_4 (Scheme 41). In this way, the occurrence of the secondary cycle is completely avoided and the enantioselectivities are comparable with those obtained under stoichiometric conditions. Furthermore, it was found that addition of methyl sulfonamide to the reaction mixture considerably accelerates the hydrolysis of osmium (VI) glycolate **137** so that the reaction time is up to 50 times shorter.[132]



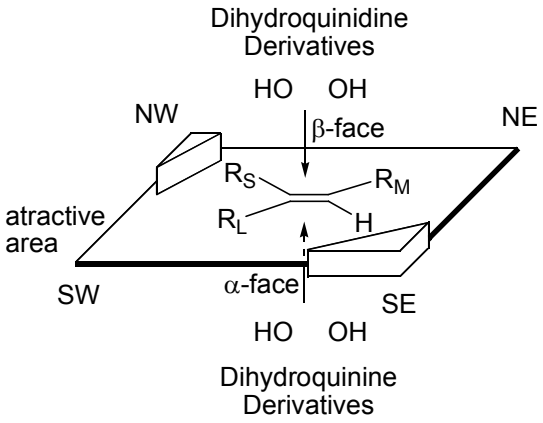
Scheme 41: Proposed Catalytic Cycle for the Heterogeneous AD Reaction.

The next major improvement involved the development of new ligands with two independent cinchona alkaloid units bridged by an aromatic or heteroaromatic moiety.[133] The two alkaloid moieties play different roles, one being responsible for the catalytic process while the other one provides the binding surface for the substrate ("chiral binding pocket for the olefin"). Over 400 different alkaloid derivatives from the first and second generation of ligands have been screened in the AD reaction and it was found that the latest ones are superior in terms of selectivity. Among them, the bis-cinchona alkaloids bearing a pyridazine (PYDZ), phtalazine (PHAL), diphenylpyrimidine (PYR) and more recently an antraquinone (AQN) core are the most effective ones (Scheme 42).



Scheme 42: Selected Dimeric Cinchona Alkaloid Derivatives.

Moreover, the absolute stereochemistry of the products can be predicted from an empirical 'mnemonic' device (Scheme 43).[134] All these developments have converged to allow the formulation of a reagent mixture called AD-mix, which contains all necessary reagents for performing the AD reaction under heterogeneous conditions.

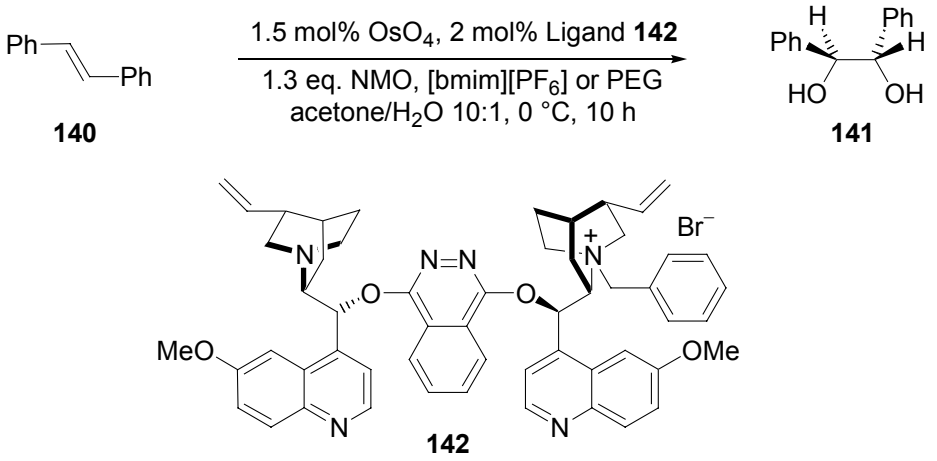


Scheme 43: Face Selection Rule for Prediction of AD Selectivity.

Concerning the reaction mechanism, two possible pathways have been proposed to rationalize the characteristic features of the reaction and are currently under investigation: a concerted [3+2][135] (the CCN model for Criegee-Corey-Noe) and a stepwise [2+2][136] pathway (Sharpless). However, recent evidence from Sharpless supports a [3+2] cycloaddition as the rate determining step.[137]

Taking into account the high cost of the chiral ligands and osmium tetroxide, extensive work is being carried out in order to replace them with reusable derivatives such as (soluble or insoluble) polymer supported ligands[138] and more recently immobilized osmium tetroxide which has been produced by microencapsulation,[139] ion-exchange techniques[140] or osmylation of resins.[141] All these approaches succeeded in recovering either the ligand or the osmium species, but failed in recycling the two components at the same time.

Zhang has developed a recyclable catalytic system based on a mono-quaternized bis-cinchona alkaloid ligand **142** and OsO_4 in combination with PEG or an ionic liquid.[142] Both catalytic components have been recycled in five consecutive AD's of *trans*-stilbene without significant loss in the selectivity and without the use of additional OsO_4 or ligand. Furthermore it was found that addition of tetraethylammonium acetate to the reaction mixture had a positive effect on the enantioselectivity.



Scheme 44: Asymmetric Dihydroxylation According to Zhang.

Recently, systems based on $RuO_4/NaIO_4$,[143] iron complexes/H_2O_2[144] as well as chiral phase transfer reagents/$KMnO_4$[145] emerged as alternatives for the well known osmylation reaction.[130]

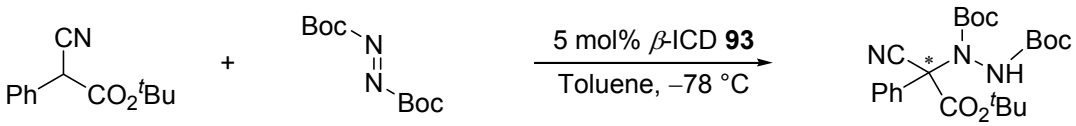
Recent advances in the field of transition metal catalyzed olefin oxidation led to the development of the second fundamental osmium-based oxidative olefin functionalization: asymmetric aminohydroxylation.[146] Within the last years both systems have found wide applications in the synthesis of chiral drugs, natural products as well as in the production of fine chemicals on a large scale.[147]

1.3.3 C-N bond formation

There is only a limited number of reports on the asymmetric construction of nitrogen substituted quaternary stereogenic centers employing cinchona alkaloids as catalysts.[148] Some are dedicated to the enantioselective synthesis of aziridines and 2H-azirines, compounds which have attracted attention due to the regio- and stereoselective ring opening reaction which they may undergo. Asymmetric aziridination of electron deficient olefins with aryl hydroxamic acids, by means of phase transfer catalysis, afforded *N*-aryl aziridines with moderate enantioselectivity (up to 62% ee). An enhancement in the optical purity could be achieved by recrystallization.

Another simple approach toward the synthesis of optically active nitrogen-containing compounds, *via C-N* bond formation, is the direct α-amination of carbonyl compounds. For example, the proline catalyzed α-amination of unmodified aliphatic ketones and aldehydes,[29] yielding useful synthons for the synthesis of amino acid derivatives was described in chapter 1.1. Bifunctional Lewis acid catalysts for the α-amination of β-ketoesters and α-substituted β-ketoesters are also known.[149] Recent reports enlarged the number of applications in this area by showing that cinchona alkaloid derivatives serve as organocatalysts in the enantioselective amination of α-substituted α-cyanoacetates.

In late 2004 Jørgensen reported the first general protocol for the direct asymmetric catalytic α-amination of cyanoacetates using commercially available azodicarboxylates as the nitrogen source and β-ICD (**93**) as catalyst.[150] Both, the rate and the asymmetric induction were highly dependent on the azodicarboxylate structure. The reaction required only a few seconds for completion when diethyl- or dibenzyl-azodicarboxylate were employed as electrophile, affording products with 84% and 64% ee respectively. Excellent enantioselectivity (>98% ee) was obtained in the amination of **143** with di-*tert*-butyl azodicarboxylate (**144**) catalyzed by 5 mol% β-ICD (**93**) in toluene at −78 °C. It is worthy of note that lowering the catalyst loading to 0.5 mol% had no influence on the yield or selectivity.



1.1 eq. **143** 1.0 eq. **144** **145**

99% y, >98% ee

Scheme 45: Cinchona Alkaloid Catalyzed Asymmetric α-Amination of Cyanoacetates.

Accordingly, a large range of α-aryl α-cyanoacetate were found to undergo a clean reaction, affording the corresponding products in excellent yields (95-99%) and high enantiomeric excesses (89->98% ee). Moreover, the reaction versatility has also been demonstrated in the reaction of various β-dicarbonyl compounds (β-ketoesters, β-diketones) with di-*tert*-butyl azodicarboxylate, providing easy access to useful chiral

building blocks. Unfortunately, any attempts to promote a highly selective amination of α-alkyl α-cyanoacetates failed, and the products were obtained in high yields but nearly racemic form.

Due to the fact that the conformationally rigid cinchona alkaloid catalyst is available in only one form (as quinidine derivative) the amination reaction provides access to only one of the two possible enantiomeric adducts. Subsequently, Deng optimized the system, and now both enantiomers are readily available by employing either the quinidine derivative **84b** or the quinine derivative **85b** as catalyst.[151]

1.3.4 C-S bond formation

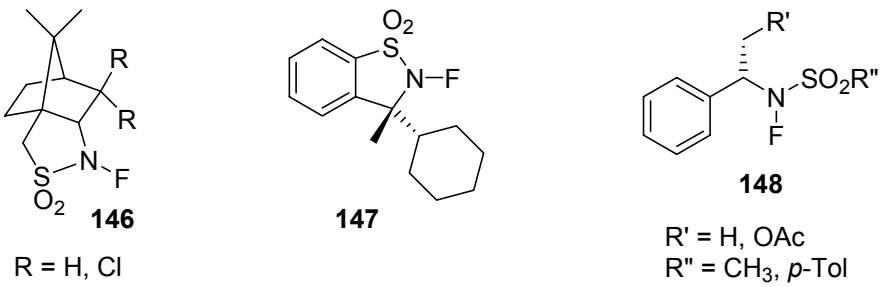
Catalytic asymmetric conjugate addition to activated olefins has attracted considerable attention because of its synthetic utility. While different strategies have been devised for the enantioselective conjugate addition of carbon nucleophiles to α,β-unsaturated ketones and aldehydes,[152] addition of heteroatom containing nucleophiles, such as nitrogen, oxygen or sulfur based nucleophiles, remains still an elusive goal. Although much effort has been made toward the development of a general and highly enantioselective 1,4-addition of thiols to activated olefins, the results still leave space for further improvement. In 1981, Wynberg reported on the stereoselective addition of aromatic thiols to cyclic enones promoted by catalytic amounts of non-modified cinchona alkaloids.[153] It is assumed that the thiol and the chiral amine base are forming an ion pair which then reacts with the enone in the rate determining step. It was found that the presence of the free hydroxyl group in the catalyst has a positive effect on the enantioselectivity. However, despite intensive optimization of the reaction parameters and careful investigation of the catalyst structure, the addition resulted in only low to moderate enantioselectivity.

Nowadays, various ethers of mono- and bis-cinchona alkaloids are commercialized since they proved to be effective over a wide range of reactions. Taking advantage of the catalyst availability, Deng developed a general protocol for the addition of 2-thionaphthol to various cyclic enones.[154] Sharpless bis-cinchona alkaloids are

responsible for the success of this reaction. Interestingly, the sense of asymmetric induction obtained with the natural cinchona alkaloid is opposite to that obtained when the corresponding bis-derivative was used in the reaction. This fact inevitably leads to the conclusion that the mechanism of this reaction differs from the one described by Wynberg.

1.3.5 C-F bond formation

Considerable attention has been paid in recent years to fluorinated molecules, and the field of organofluorine chemistry is growing rapidly. Fluorinated compounds are of great interest not only in chemistry, but also medicinal and material science.[155] Hence, the development of efficient methodologies for their stereoselective synthesis is now demanded. Although several successful approaches are known for their diastereoselective synthesis,[156] the enantioselective fluorination is still a challenging field. The first direct enantioselective fluorination was reported in 1988, and various *N*-fluorocamphorsultams[157] were employed as source of chirality. Despite only moderate results being obtained, this was the first report on the reagent-controlled asymmetric fluorination reaction involving an electrophilic fluorine atom. In order to improve the enantioselectivity, new chiral electrophilic fluorinating agents have been designed (Scheme 46).[158] Generally, the new reagents were more efficient and enantioselectivities with up to 88% ee have been attained with Takeuchi's saccharin-based fluorinating agent **147**. However, these protocols seem not attractive in view of preparative aspects due to the tedious catalyst synthesis ending with the N-F bond formation by means of either toxic molecular fluorine or explosive gaseous perchloryl fluoride.

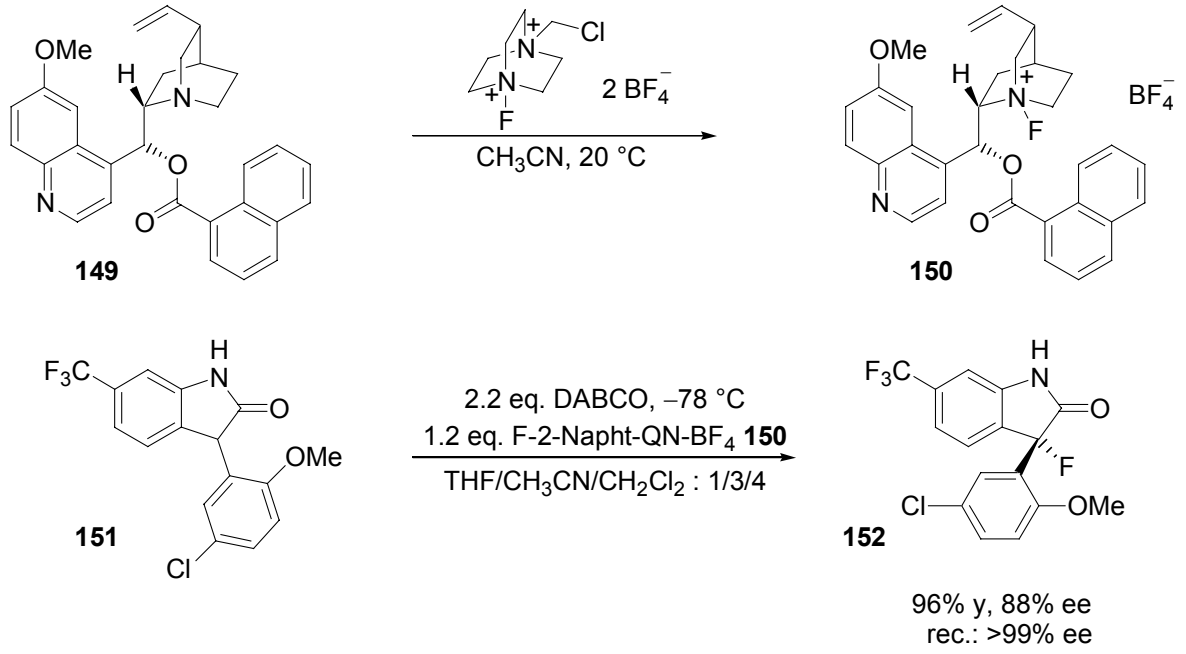


Scheme 46: First Generation of Chiral Fluorinating Reagents.

Independently, Shibata[159] and Cahard[160] reported on the development of an efficient direct fluorination method based on the use of stoichiometric amounts of cinchona alkaloid *N*-fluoro ammonium salts. These chiral reagents, capable of selective fluorine cation delivery, were synthesized according to Bank's fluorine-transfer procedure.[161] Complete fluorine transfer from the commercially available achiral reagent Selectfluor (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis tetrafluoro-borate)[155d] to the cinchona alkaloid was achieved within 30 min in acetonitrile, as determined by ^{19}F-NMR analysis of the reaction mixture. Ketones and ketoesters were typical substrates evaluated in the reaction.

Two equivalents of base were necessary in order to avoid protonation of the *in situ* generated enolate by the free OH group of the alkaloid. Furthermore, protection of the hydroxyl group was found to be crucial for achieving high enantioselectivities. Regarding the influence of the *O*-substituent, reagents bearing a bulkier protecting group were found to be superior in terms of selectivity. Moreover, the degree of asymmetric induction exhibited by these preformed reagents was strongly dependent on the reaction conditions. A considerable increase in enantioselectivity has been observed when silyl enol ethers were used as substrates (61-84% ee vs 33-50% ee). This new approach involving silyl enol ethers is more convenient than the fluorination of metal enolates since no base is required for the *in situ* enol formation.

Next, the usefulness of this new protocol was demonstrated by the enantioselective synthesis of MaxiPost, a potent potassium channel opener.[162] Reaction of oxindole **151** with the *N*-fluoroammonium salt **150**, in the presence of DABCO as base, yielded the desired product **152** in excellent yield and with high enantiomeric excess (96% y, 88% ee). A single recrystallization afforded optically pure material (>99% ee). Previously, the two enantiomers have been separated by chiral HPLC resolution of the racemic mixture.



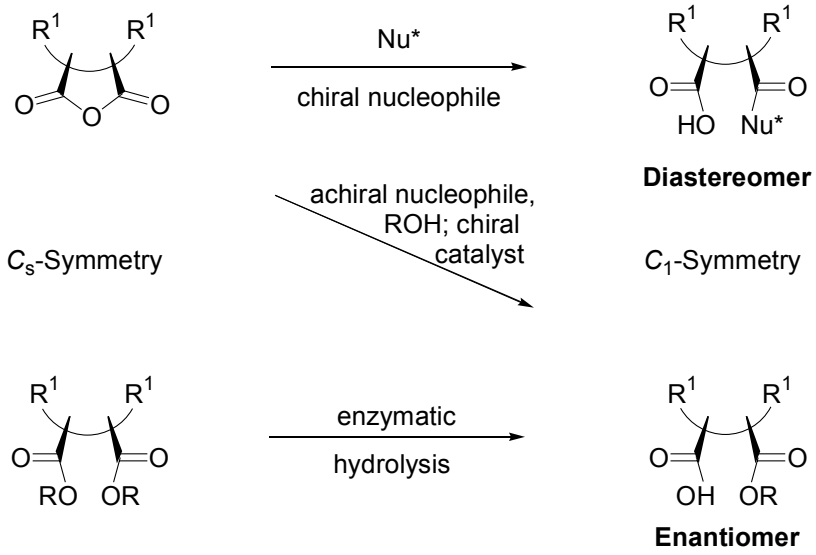
Scheme 47: Enantioselective Synthesis of MaxiPost According to Cahard.

While Cahard's protocol makes use of preformed cinchona alkaloid ammonium salts, Shibata prefers the *in situ* generation of the active fluorinating species.[159] The order of addition was found to be crucial in order to achieve enantioselective fluorination. Addition of Selectfluor to a mixture of alkaloid and enolate resulted in racemic product. This means that an alkaloid/enolate complex cannot be responsible for an enantioselective process. On the other hand, satisfactory results were obtained when Selectfluor and the alkaloid were combined before the addition of the substrate. ^{19}F-NMR and X-ray crystal structure analysis are in agreement with Cahard's studies and supports the formation of a new active species by fluorination of the cinchona alkaloid. This also explains why only stoichiometric amounts of alkaloid assure a successful reaction and why any attempts toward a catalytic version failed.

It was Park who first reported a catalytic enantioselective electrophilic fluorination of indanone and tetralone, by means of phase transfer catalysis.[163] Slow addition of the $(PhSO_2)_2NF$ to the preformed enolates in the presence of 10 mol% chiral phase transfer catalyst afforded the α-fluoro-β-keto esters in high yields (74-94%) and with moderate enantiomeric excesses (41-69% ee).

1.4 Asymmetric anhydride opening

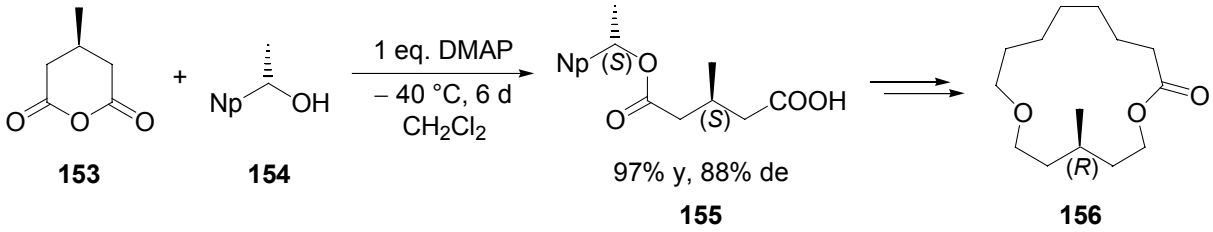
Desymmetrization of *meso*-dicarbonyl compounds to yield chiral products proved to be a powerful synthetic tool in asymmetric synthesis since it allows the formation of multiple stereogenic centers in one symmetry breaking operation.[164] For this purpose, both enzymatic and chemical approaches have been extensively investigated (Scheme 48). For example, starting from symmetrically substituted diesters, desymmetrization with the help of enzymes provides optically active hemiesters which are valuable building blocks for the synthesis of natural products or biologically active substances.[165] PLE is known to selectively catalyze the enantiotopos-differentiating hydrolysis of over 400 prochiral dicarboxylic acid diesters and diol diacetates.[165d] Unfortunately, the enzymatic approach is generally limited to the synthesis of only one enantiomer. In contrast, the desymmetrization of *meso*-anhydrides is not limited by this restriction since often the chiral reagent or mediator involved in the reaction is available in both enantiomeric forms.[166]



Scheme 48: Desymmetrization of *meso*-Dicarbonyl Compounds.

1.4.1 Chiral nucleophiles

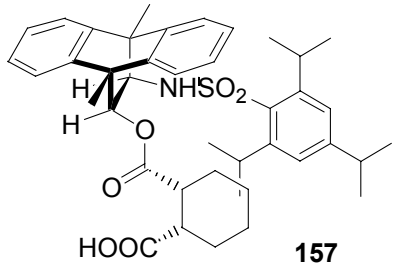
Several reports have been made on the addition of chiral alcohol or amine nucleophiles to *meso*-anhydrides. One of the most successful systems was reported by Heathcock and involves the addition of (*S*)-1-naphthylethanol to 3-substituted glutaric anhydrides.[167] A de of 88% was observed in the case of 3-methylglutaric anhydride and the product has found application in the synthesis of a new powerful oxamacrolide musk odorant (Scheme 49).[168]



Scheme 49: Diastereoselective Ring Opening of 3-Methyl Glutaric Anhydride According to Heathcock.

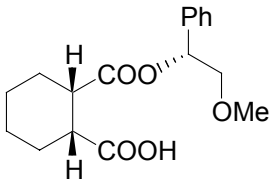
Mukaiyama reported on the desymmetrization of bicyclic *meso*-anhydrides with (*R*)-2-methoxy-1-phenylethanol diphenylborate, affording the corresponding hemiesters in good yields (75-95%) and moderate to excellent diastereoselectivities (40-99% de).[169]

Kunieda has attained high diastereoselectivity in the ring opening of a variety of bi- and tricyclic anhydrides by using lithium complexes generated *in situ* from various sterically hindered chiral *N*-sulfonylamino alcohols.[170] A significant increase in the diastereoselectivity was observed when hexamethylphosphoric triamide (HMPA) was employed as additive. For example, the cyclohexane hemiester **157** was obtained in 93% yield and 99% de by using the lithium salt of the corresponding bulky 2,4,6-triisopropylbenzenesulfonyl amino alcohol and 5 eq. of HMPA at −78 °C in THF. Interestingly, the use of the zinc salt as nucleophile resulted in the opposite sense of asymmetric induction. Accordingly, either diastereomer could be selectively synthesized by using different metal salts of the same chiral amino alcohol.



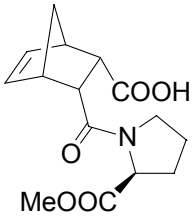
157

93% y, 99% de



158

90% y, 99% de



159

91% y, 98% de

Scheme 50: Representative Diastereoselective Anhydride Desymmetrizations.

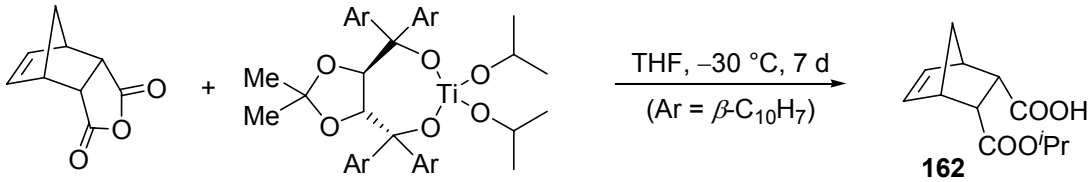
North reported on the desymmetrization of *endo*-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride using proline esters as chiral nucleophiles.[171] The process has been successfully applied to the synthesis of peptides and pseudopeptides incorporating an *endo*-(2*S*,3*R*)-norborn-5-ene residue. Unfortunately, proline cannot be cleaved and replaced by other amino acids so that this synthetic approach is limited to molecules containing proline at the first position of one peptide strand. In addition, the protocol suffers from strong substrate limitations in that any attempts to extend the methodology to bicyclic anhydrides resulted in poor or no asymmetric induction.

Despite several attempts toward a highly diastereoselective process, no general protocol, with respect to anhydride structure, could be elaborated. Consequently, the enantioselective alcoholysis emerged as an attractive alternative.

1.4.2 Enantioselective desymmetrization using chiral Lewis acids

Seebach investigated the Lewis acid-mediated transfer of an isopropoxy group from the chiral ligand sphere of Ti-TADDOLate to cyclic *meso*-anhydrides to afford the corresponding hemiesters.[172] Unlike the previously described protocols, which give products with covalently linked chiral auxiliaries, Seebach's system delivers directly enantiomerically enriched hemiesters. The system was optimized for the norbornene anhydride and the best results (88% y, 98% ee) were obtained at –30 °C in THF, using β-naphthyl-titanium TADDOLate derivative **161** as mediator. A large variety of tricyclic anhydrides have been functionalized under these conditions, affording

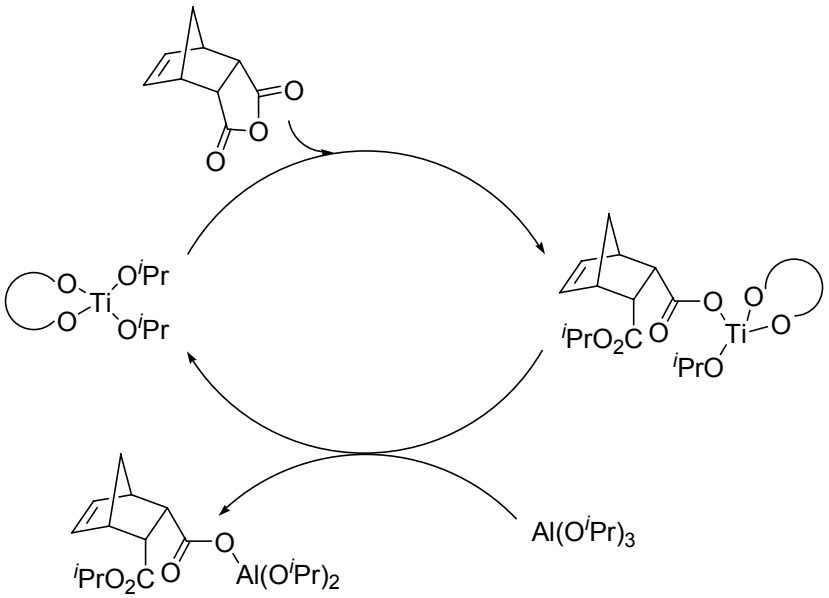
products in high yields (82-92%) and with excellent enantiomeric excesses (94-98% ee). Slightly higher temperatures were required in the case of less reactive bicyclic anhydrides, leading to products in good yields (59-87%) and with high enantiomeric excesses (88-96% ee). Unfortunately, only unsatisfactory results were obtained when mono- and disubstituted glutaric anhydrides were subjected to the alcoholysis reaction.



160 1.2 eq. **161** **162** 88% y, 98% ee

Scheme 51: Enantioselective Anhydride Opening According to Seebach.

In addition, a catalytic protocol which permits the substoichiometric use of Ti-TADDOLate in the presence of stoichiometric amounts of $Al(O^iPr)_3$ was developed.[172b] The proposed catalytic cycle is outlined in Scheme 52. It was assumed that if the rate of the Ti-TADDOLate catalyzed enantioselective alcoholysis is much greater than the rate of the $Al(O^iPr)_3$ catalyzed racemic alcoholysis, then the ee of the hemiester can be retained, while $Al(O^iPr)_3$ regenerates the chiral catalyst *via* metal-ligand exchange. Accordingly, hemiester **162** was obtained in 74% yield and 96% ee by using a catalytic amount of Ti-TADDOLate (20 mol%) and a stoichiometric amount of aluminum isopropoxide. Unfortunately, the catalytic process now required an extremely long reaction time (24 days) and was less successful when applied to other substrates.

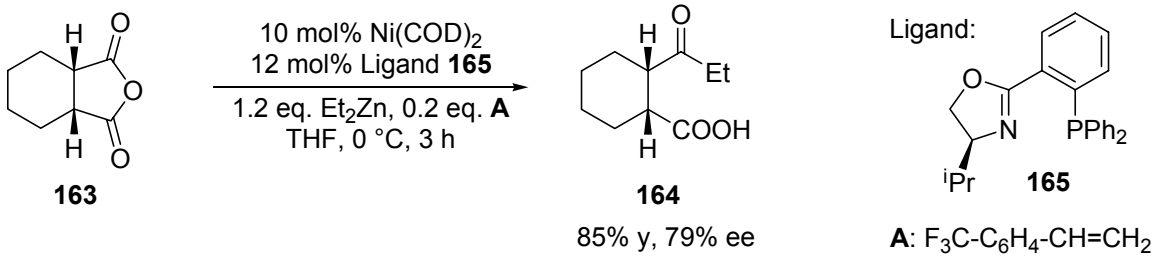


Scheme 52: Proposed Mechanism for the Substoichiometric use of Ti-TADDOLate.

Subsequently, the methodology was extended to the ring opening of *meso*-sulfonylimides to give the corresponding sulfonylamido isopropyl esters with up to 98% ee.[173] The Ti-TADDOLate mediated kinetic resolution of racemic dioxolanones, azlactones, and biaryllactones leading to highly enantioenriched products was also described.[174]

Recently, the interest in the development of general and selective desymmetrization methods has increased considerably and along with the well-known concepts described above, new approaches for the ring opening reaction, involving carbon-based nucleophiles, have been reported. Detailed studies on the alkylation of cyclic *meso*-anhydrides catalyzed by a nickel complex have been described by Rovis.[175] Several phosphine ligands were initially tested in combination with $Ni(COD)_2$ in the addition of diethylzinc to cyclohexanedicarboxylic anhydride. The mechanistic pathway involves firstly an oxidative addition of the low-valent nickel complex to the electron deficient C-O bond of the anhydride. The resulting organometallic species then undergoes transmetalation with the zinc reagent to provide the key intermediate, which upon reductive elimination affords the product and regenerates the catalyst. The use of electron-deficient olefins as promoters for the reductive elimination increased the yield and the reaction rate considerably. For example the addition of

$ZnEt_2$ to anhydride **163** is 250 times faster in the presence of 10 mol% *p*-trifluoromethylstyrene and affords the product in 80% yield in less than five minutes. Concerning the influence of the ligand structure on the reaction efficiency, it was found that bidentate phosphine ligands are superior to trialkyl- and triarylmonodenate ones. Moreover, the reaction is highly general with respect to the substrate, and a large variety of mono-, di-, and tricyclic anhydrides have been reacted with $ZnEt_2$ to give the corresponding γ- and δ-keto acids in moderate to excellent yields (61-96%). In addition, the use of Pfaltz N,P-ligand **165** afforded an active catalyst for the enantioselective alkylation of cyclohexane dicarboxylic anhydride **163** and provided the γ-keto acid **164** in 85% yield and 79% ee.



163 **164** 85% y, 79% ee **165**

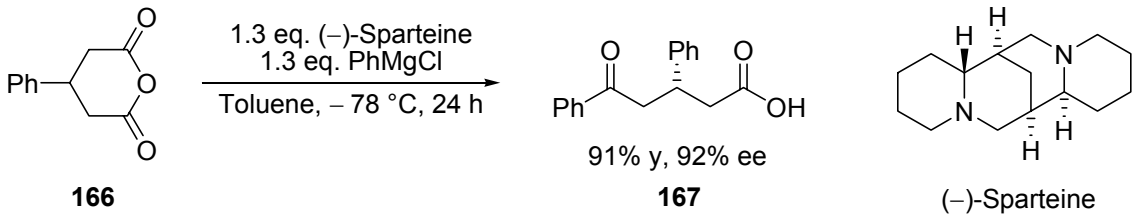
A: $F_3C\text{-}C_6H_4\text{-}CH{=}CH_2$

Scheme 53: Enantioselective Ring Opening with *C*-based Nucleophile According to Rovis.

An improved protocol for the asymmetric anhydride desymmetrization has also been developed. Room temperature palladium-catalyzed diphenylzinc addition to structurally diverse cyclic anhydrides provided the corresponding keto acids in good yields (61-89%) and high enantioselectivities (89-97% ee).[176]

A second useful transformation involving carbon-based nucleophiles was reported by Fu.[177] It was found that commercially available (–)-sparteine promotes an enantioselective ring opening reaction of 3-phenyl glutaric anhydride (**166**) by phenyl magnesium chloride (PhMgCl), leading to the corresponding δ-keto acid **167** in 63% yield and 88% ee. A significant improvement in the yield (91%) and selectivity (92% ee) was observed when a slight excess of Grignard reagent/(–)-sparteine was employed as source of chirality (Scheme 54). The reaction proved to be general with respect to the substrate, and various 3-substituted glutaric anhydrides were

converted into the corresponding keto acids in good yields (51-91%) and high enantioselectivities (87-92% ee).



166 **167** (–)-Sparteine

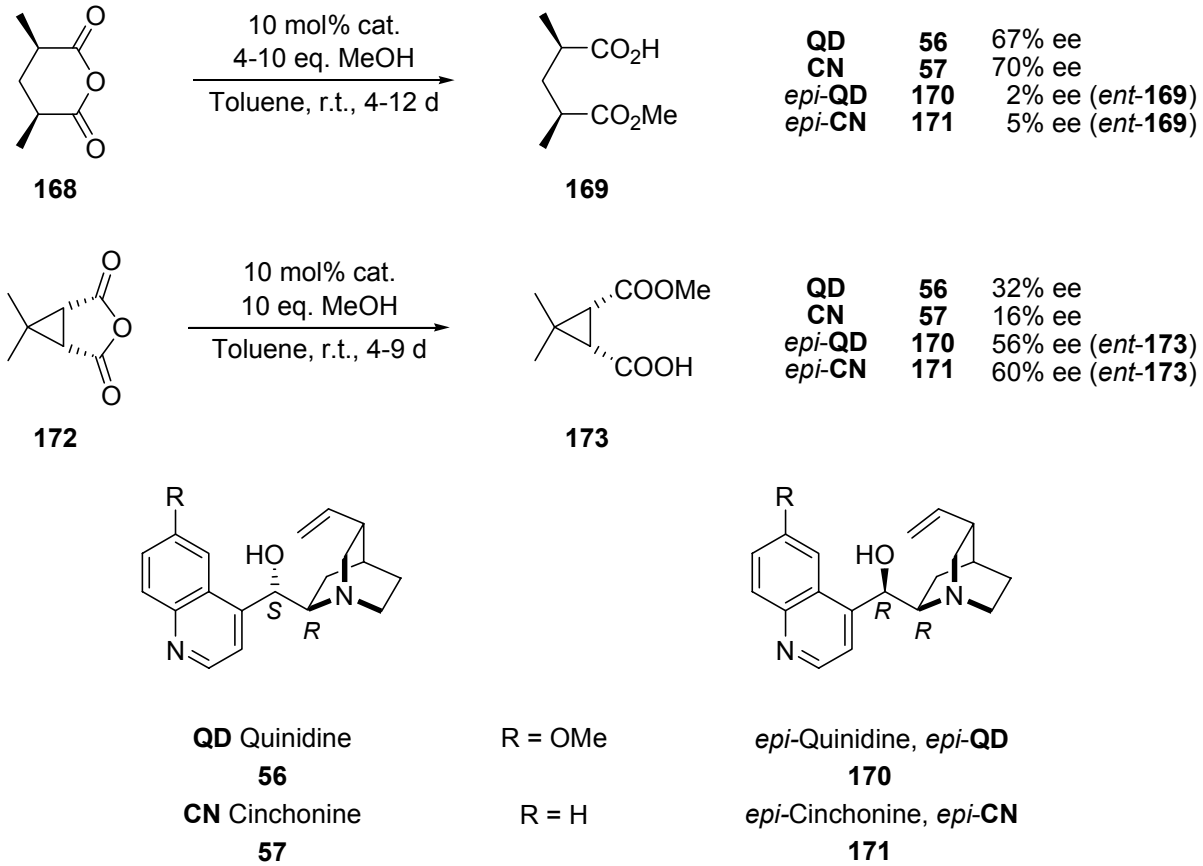
Scheme 54: Enantioselective Ring Opening with *C*-based Nucleophile According to Fu.

1.4.3 Enantioselective desymmetrization with chiral Lewis bases

Much progress has also been made on the metal free anhydride desymmetrization, the first results being reported in the late 80's by Oda[178] and Aitken[179] independently. A large variety of cyclic *meso*-anhydrides were functionalized and the corresponding half-esters were obtained in high yield and with moderate enantioselectivities by using a catalytic amount of cinchona alkaloids. While Oda's studies dealt with the desymmetrization of mono- and bicyclic anhydrides, Aitken extended the substrate scope to more complex tri- and tetracyclic anhydrides.

Oda investigated the influence of the catalyst structure on the reaction selectivity and the sense of asymmetric induction. Glutaric and succinic anhydrides were examined in the reaction with methanol, as nucleophile, in the presence of 10 mol% cinchona alkaloid. The products were obtained in high yields but with low to moderate enantiomeric excesses. The enantioselectivity was found to be strongly dependent on specific substrate/catalyst combinations. Generally, the naturally occurring cinchona alkaloids (*erythro* bases) were more active and selective than their C_9-epimers (*threo* bases) in the desymmetrization of glutaric anhydrides, affording the products with up to 70% ee. On the other hand, the *erythro* bases exhibited lower asymmetric induction compared to the *threo* bases for the five-membered ring anhydrides (Scheme 55). Furthermore, it was found that the reaction stereochemistry is entirely controlled by the configurations at C_8 and C_9 in the catalyst and it was

demonstrated that quinuclidine catalyzes the reaction to the same extent as cinchonine, whereas quinoline showed almost no activity. The involvement of a catalyst/substrate ion-pair complex in the determination of the stereochemical outcome of the reaction was excluded and a general-base catalysis mechanism (with the quinuclidine nitrogen being responsible for the catalytic activity) was rationalized. The first order dependence of the reaction rate on the alcohol nucleophile, the deuterium isotope effect and the fact that the more acidic 2,2,2-trifluoroethanol was more reactive than ethanol all pointed toward a general-base catalysis mechanism.

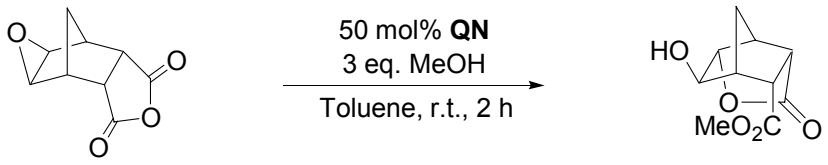


Scheme 55: Cinchona Alkaloid Mediated Ring Opening According to Oda.

A similar reaction protocol was developed by Aitken.[179a] Room temperature methanolysis of *meso*-epoxyanhydride **174** in the presence of 10 mol% quinine in toluene, followed by intramolecular epoxide opening led to the lactone **175** in 80% yield and 38% ee. An increase in the catalyst loading to 50 mol% afforded the lactone with 76% ee (Scheme 56). In addition, a single recrystallization furnished

enantiomerically pure product (>99% ee). Since lactone **175** is acid sensitive, in order to avoid possible difficulties which could occur during the acidic workup, polymer supported cinchona alkaloids, prepared by copolymerization with acrylonitrile, were next examined. The reaction was found to be efficient, but always occurred with lower selectivity compared to the non-polymeric catalysts.

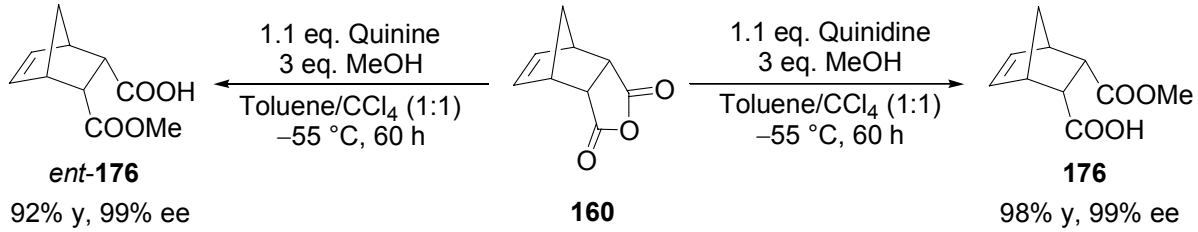
Under the same reaction conditions (10-50 mol% catalyst, 3 eq. MeOH, r.t., toluene, 24 h), several norbornane type anhydrides afforded the corresponding methyl hemiesters in good yields (69-97%) with moderate enantiomeric excesses (35-67% ee).[179b]



174 **175**
57% y, 76% ee

Scheme 56: Cinchona Alkaloid Mediated Ring Opening of Epoxyanhydride **174** According to Aitken.

Based on Oda's and Aitken's pioneering studies, an improved protocol was developed by Bolm which allowed a wide range of structurally diverse methyl hemiesters to be prepared with up to 99% yield and 99% ee (Scheme 57).[180] Low temperature, an excess of methanol and a stoichiometric amount of the inexpensive and readily available cinchona alkaloid constituted the key for a highly efficient ring opening reaction. Compared to the existing methods, this new protocol proved to be very simple and more convenient to perform. After reaction, the alkaloids can be recovered quantitatively and reused without loss of enantioselectivity. In addition, a catalytic protocol which gives comparable results and involves the use of 0.1 eq. quinidine and 1 eq. of an achiral sterically hindered tertiary amine base such as pempidine, was described.[180b]



ent-**176**
92% y, 99% ee

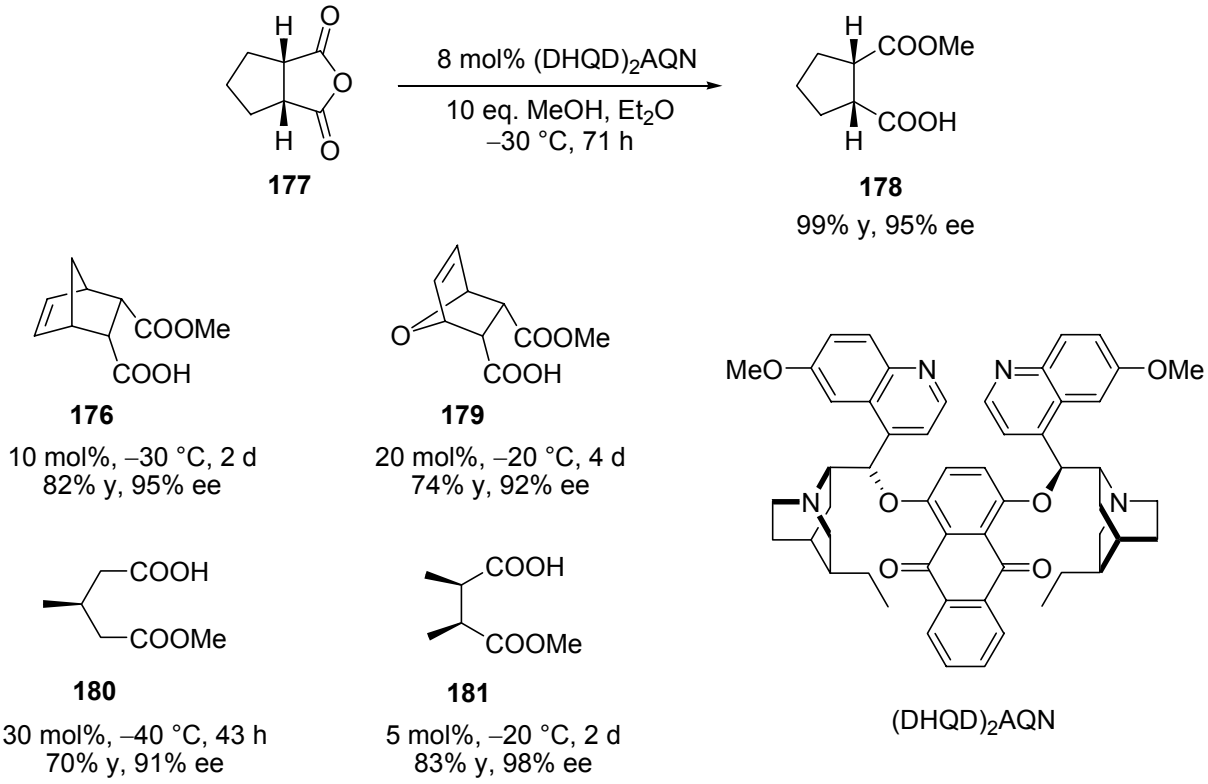
160

176
98% y, 99% ee

Scheme 57: Anhydride Desymmetrization According to Bolm.

It is remarkable that the process has found immediate application in the synthesis of β-amino acids,[181] γ-amino alcohols[182] and 1,2-diamines.[182,183] The methodology was also successfully applied in other groups, as for example: by Carreira in the synthesis of the cyclopentyl core of the axinellamines,[184] by Bernardi in the synthesis of both enantiomers of *trans*-cyclohex-4-ene-1,2-dicarboxilyc acid on a multigram scale,[185] by Tanyeli in the synthesis of a chiral norbornane-type 1,4 diamine,[186] and more recently by Keen in the synthesis of an $\alpha_v\beta_3$ antagonist.[187]

Comparable results were subsequently obtained by Deng, who found that commercially available mono and bis-cinchona alkaloid derivatives are also capable of functioning as effective chiral Lewis base/nucleophilic organic catalysts in the ring opening reaction.[188] These modified cinchona alkaloids have been previously used by Sharpless as ligands in the asymmetric dihydroxylation and aminohydroxylation reaction. Screening of various aryl ethers and esters of cinchona alkaloids in the asymmetric alcoholysis reaction showed that the dihydroquinidine-based catalysts, DHQD-PHN and $(DHQD)_2AQN$, possess a remarkable ability to promote a highly enantioselective reaction. A large range of bi-, and tricyclic anhydrides underwent ring opening reaction with methanol (10 eq.) at –20 or –30 °C in ether in the presence of 5-20 mol% $(DHQD)_2AQN$, affording the corresponding methyl hemiesters in high yields (74-99%) and with excellent enantioselectivities (92-98% ee).



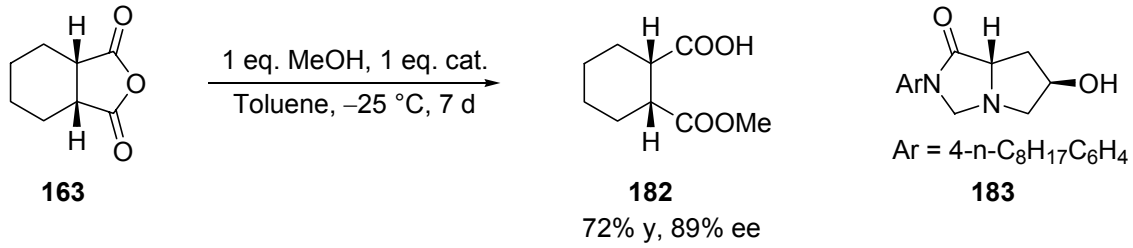
Scheme 58: Biscinchona Alkaloid Catalyzed Methanolysis of Cyclic Anhydrides.

Notable, with $(DHQD)_2AQN$ (5-30 mol%) as catalyst, even the monocyclic anhydrides were readily converted into enantiomerically enriched (90-98% ee) acyclic hemiesters. Furthermore, the anhydride desymmetrization has been applied as a key step in the catalytic asymmetric synthesis of (+)-Biotin.[189] Recent studies by Deng[190] revealed that the biscinchona alkaloids are able to efficiently mediate the kinetic resolution of racemic cyclic anhydrides[190a] and *N*-carboxy anhydrides,[190b] as well as the dynamic kinetic resolution of *N*- and *O*-carboxy anhydrides.[190c,d]

A polymer supported $(DHQD)_2AQN$ catalyst has been recently introduced and evaluated in the asymmetric ring opening reaction of cyclohexene dicarboxylic anhydride by Wöltinger.[191] By means of a repetitive batch system it was possible to run the reaction over 18 cycles achieving a conversion of >95% for each cycle. However, the synthetic usefulness of the process is limited since it was only optimized for a single substrate and the ee decreased drastically, from almost 90 to

60%, during the first 5 runs. Silica gel-supported quinidine as heterogeneous catalyst for the anhydride desymmetrization, was synthesized and optimized for the same substrate by Carloni.[192] More efficient heterogeneous chiral organocatalysts were introduced by Han,[193] who demonstrated that silica gel-supported bis-cinchona alkaloids exhibited higher catalytic activity in comparison to Carloni's system. In addition, they are applicable to a wider substrate spectrum and give products with up to 92% ee.

Uozumi focused his attention on the use of noncinchona-based catalysts for the enantioselective anhydride desymmetrization.[194] A library of five *N*-chiral bicyclic tertiary amines was synthesized and tested in the methanolysis of cyclohexane dicarboxylic anhydride. The methyl hemiester **182** was obtained in 72% yield and 89% ee when stoichiometric amounts of methanol, as nucleophile, and pyrrolo-imidazolone derivative **183**, as chiral catalyst, were used in the reaction. Lowering the amount of catalyst to 10 mol% afforded the product in poor yield (33%) and 65% ee.



163 **182** 72% y, 89% ee **183**

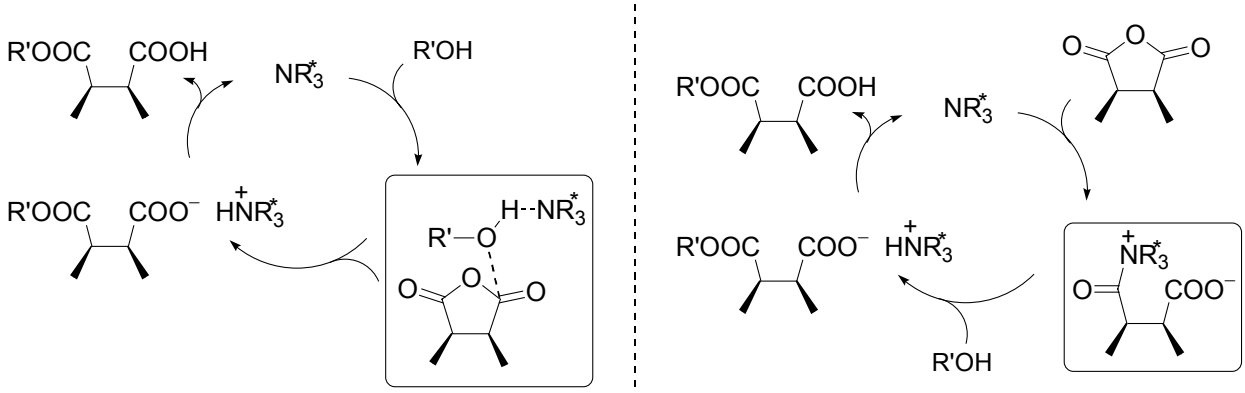
Scheme 59: Desymmetrization of *meso*-Cyclic Anhydrides According to Uozumi.

The 5-step procedure for the catalyst synthesis,[194,195] the limited substrate spectrum (only 3 examples including **163**) and the moderate reaction selectivity mark the system as inconvenient from practical and synthetic point of view.

1.4.4 Mechanistic studies

The mechanism of the alkaloid-mediated ring opening has not been fully elucidated yet. So far, two general models are discussed,[196] although neither provides a clear explanation for the source of distinction between the enantiotopic carbonyl groups. On the one hand, a nucleophilic catalysis is suggested in which the quinuclidine nitrogen atom of the alkaloid attacks the anhydride at one of the carbonyl groups[179b,180b] to give an acylammonium salt as intermediate. Subsequent nucleophilic attack by the alcohol yields the product and regenerates the catalyst (Scheme 60, B). This mechanism is similar to the one accepted for the amine-catalyzed kinetic resolution of secondary alcohols by acylation.[197]

On the other hand, the alkaloid could serve as chiral base for the alcohol molecule.[178a] Formation of a hydrogen bonding complex activates the alcohol, enabling it to attack the anhydride (Scheme 60, A). The resulting ion pair undergoes proton transfer, forming the hemiester and regenerating the chiral catalyst. This proposal corresponds to the one suggested by Wynberg for the asymmetric addition of thiols to enones.[198]



Scheme 60: Proposed Mechanisms for the Amine-Catalyzed Alcoholysis of *meso*-Anhydrides.

Evidence has been found for both models. Thus the kinetic isotope effect (k_{MeOH}/k_{MeOD} = 2.3) observed by Oda and co-workers[178a] supports the latter, whereas Carloni's detection of an anhydride-quinidine adduct by mass spectroscopy[192] indicates the formation of an acylammonium-type intermediate.[199]

2 Aim of the project

As already described in chapter 1.4.3, Bolm and co-workers developed a general strategy for the anhydride desymmetrization and after extensive optimization, a highly efficient protocol for the enantioselective methanolysis has been elaborated. As part of these studies, one target in the beginning of the present work was to further investigate the effect of different alcohol nucleophiles on the reaction rate and selectivity. Since the deprotection of the methyl ester moiety by saponification encountered small difficulties for specific substrates during derivatization, the possibility of introducing ester functionalities which are cleavable under very mild conditions was of particular interest. Subsequently, the possibility of performing the reaction in a non-toxic, non-halogenated solvent system as well as the possibility of scaling-up the reaction without affecting its conversion and enantioselectivity should also be investigated. Finally, an additional focus of attention lay on the application of this improved desymmetrization protocol toward the synthesis of optically active β-amino acids and new C_2- and C_1- symmetric bisoxazolines which could serve as chiral ligands in the asymmetric catalysis.

3 Results and discussions

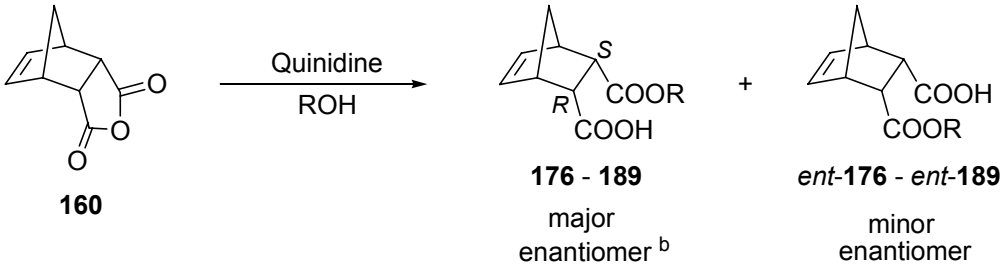
3.1 Asymmetric anhydride opening

3.1.1 Investigation of different nucleophiles

It has already been established that careful choice of the solvent system, optimal temperature and mediator had a remarkable effect on the methanolysis of various bi-, and tricyclic anhydrides, affording products in 61-99% yield and excellent enantioselectivities (85-99% ee in the case of quinidine).[180b] In view of the synthetic utility of this methodology, the possibility of introducing various ester functionalities was studied at the beginning of this project. With the norbornene anhydride as model substrate and carrying out the reactions under the previously optimized conditions we have evaluated now different alcohol nucleophiles in the asymmetric ring opening reaction and the results are summarized in Table 1.[200]

In agreement with the preliminary investigations,[180b] the steric properties of the nucleophile had a great influence on the rate and selectivity of the anhydride opening. Among all tested nucleophiles, methanol was the most selective one (Table 1, entry 1). Ethanol showed a significantly lower reactivity and selectivity when compared to methanol.[178a] Accordingly, the reaction time had to be increased from 60 to 108 h for achieving complete conversion when methanol was substituted by ethanol as the nucleophile (Table 1, entry 2). On the other hand, with 2,2,2-trifluoroethanol the reaction rate was high, but it led to a racemic product (Table 1, entry 3). This result was analogous to the findings of Oda,[178a] who also found a significant decrease in ee when 2,2,2-trifluoroethanol was employed as nucleophile. It contrasted, however, the observations made by Deng in his studies on the parallel kinetic resolution of monosubstituted succinic anhydrides.[190a] There, the highest enantiomeric excesses were achieved when the fluorinated alcohol was used as nucleophile.

Table 1: Quinidine-Mediated Opening of Anhydride **160** using Different Alcohols[a]



160

176 - **189** major enantiomer [b]

ent-**176** - *ent*-**189** minor enantiomer

Entry	Alcohol	Hemiester	ee (%)[c]	Yield (%)
1	Methanol	**176**	99	99
2	Ethanol	**184**	89	97[d]
3	2,2,2-Trifluoroethanol	**185**	rac.	96
4	Allyl alcohol	**186**	97	97
5	Propargyl alcohol	**187**	79	97
6	Benzyl alcohol	**188**	97	92
7	Benzyl alcohol	*ent*-**188**[e]	96	93
8	*p*-Anisyl alcohol	**189**	97	93

[a] All reactions were performed at −55 °C for 60 h using 1.1 eq. of quinidine and 3.0 eq. of alcohol in a toluene/CCl_4-mixture (1:1), 0.2 M solution related to anhydride. [b] For determination of the absolute configuration, see text and ref. 180b. [c] Determined by GC-analysis of the corresponding lactone using a chiral stationary phase. [d] Complete conversion was only achieved after 108 h. [e] Quinine was used as chiral mediator.

Unlike methanol and ethanol, almost no reaction took place with more sterically hindered alcohols such as 2-propanol, even when they were used as solvent. Surprisingly, allyl alcohol exhibited selectivity comparable to methanol, affording the product in 97% yield and 97 % ee (Table 1, entry 4). Since the irreversible Pd(0)-catalyzed transfer of allyl to weakly basic morpholine offers the possibility of a mild cleavage of allylic esters,[190c,201] the synthesis of **186** with 97% ee already fulfilled our initial criteria. However, taking into account the potentially tedious product purification in an amino acid synthesis (see also chapter 3.2.2) this ester functionality appeared not advantageously enough.[202] We therefore decided to focus our attention on the establishment of a benzyl ester functionality.

Thus, using benzyl alcohols as nucleophiles, hemiesters **188** and **189** were obtained in high yields (92 and 93% respectively, Table 1, entries 6, 8) and in analytically pure form with 97% ee. In contrast to the nucleophiles described so far, the required excess of the alcohol could not completely be removed in vacuum after terminating the reaction. Nevertheless, the preparative advantage of a simple workup without chromatographic purification was maintained for most products. Thus, an acidic wash permitted the recovery of the alkaloid and a subsequent mild basic extraction removed the remaining benzyl alcohol. Furthermore, benzyl hemiester **188** crystallizes nicely from ether, allowing the enantiomeric excess to be increased from a single recrystallization to >99% in only a few hours.

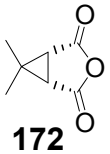
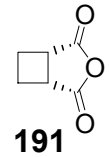
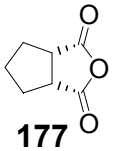
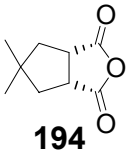
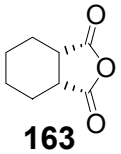
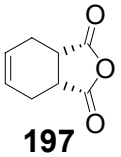
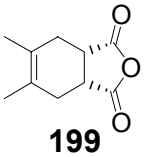
Pseudoenantiomeric quinine generated *ent*-**188** with 96% ee (Table 1, entry 7). The ease of the benzyl ester deprotection by simple hydrogenation performed after derivatization reactions broadens the applicability of the alkaloid-mediated anhydride opening favorably and encouraged us to evaluate the scope of the benzyl alcoholysis.

3.1.2 Variation of the substrate

Since the monocyclic anhydrides were not suitable substrates for the methanolysis,[180b,182] they were not included in our present research project, and we focused our attention on bi- and tricyclic anhydrides. Under the conditions optimized in our primary investigation,[180] a large variety of bicyclic anhydrides were converted with benzyl alcohol into the corresponding products in high yields and with excellent enantioselectivities (Table 2).

As previously observed, quinidine-mediated ring openings furnished monoesters with slightly higher enantiomeric excesses in comparison to the quinine mediated ones. We were pleased to see that this difference was rather low with benzyl alcohol as nucleophile (Δee benzylester enantiomers = 1-4%). Remarkably, in most of the cases the benzyl hemiesters were furnished with slightly higher enantiomeric excesses compared to their methyl analogues.

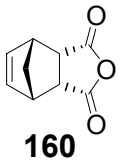
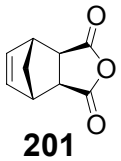
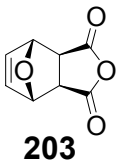
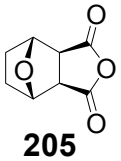
Table 2: Quinidine- and Quinine-Mediated Opening of Bicyclic *meso*-Anhydrides[a]

		Quinidine-Mediated			Quinine-Mediated		
Entry	Anhydride	Ester	ee (%)[b]	Yield (%)	Ester	ee (%)[b]	Yield (%)
1	 **172**	**190**	92	95	*ent*-**190**	88	94
2	 **191**	**192**	93	90	*ent*-**192**	90	85
3	 **177**	**193**	97	93	*ent*-**193**	95	89
4	 **194**	**195**	97	78[c]	*ent*-**195**	95	83[c]
5	 **163**	**196**	95	88	*ent*-**196**	93	84
6	 **197**	**198**	94	84	*ent*-**198**	95	84
7	 **199**	**200**	98	88	*ent*-**200**	97	87

[a] All reactions were performed at −55 °C for 60 h using 1.1 eq. of alkaloid and 3.0 eq. of benzyl alcohol in a toluene/CCl_4-mixture (1:1); for quinidine: 0.2 M with respect to the anhydride, for quinine: 0.05 M. [b] Determined by GC-analysis of the corresponding lactones using a chiral stationary phase. [c] After chromatographic purification (see experimental section).

This effect was more pronounced especially for the quinine mediated reactions, where the variation Δee (benzylester/corresponding methylester) was established between 2 and 6% for the bicyclic anhydrides.

Table 3: Quinidine- and Quinine-Mediated Opening of Tricyclic *meso*-Anhydrides[a]

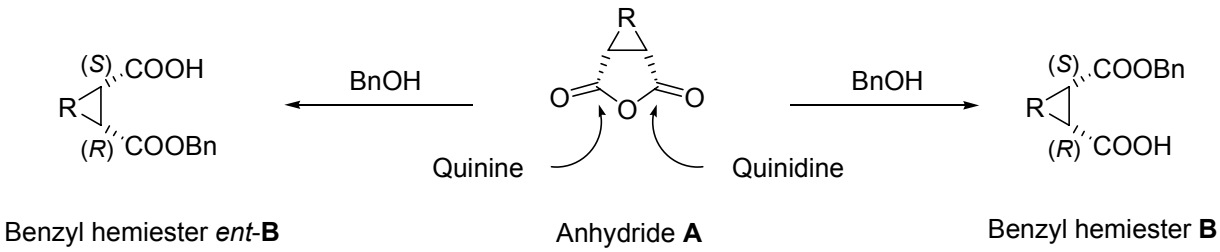
		Quinidine-Mediated			Quinine-Mediated		
Entry	Anhydride	Ester	ee (%)[b]	Yield (%)	Ester	ee (%)[b]	Yield (%)
1	 **160**	**188**	97	92	*ent*-**188**	96	93
2	 **201**	**202**	96	95	*ent*-**202**	92	81
3	 **203**	**204**	99	84[c]	*ent*-**204**	94	77[c]
4	 **205**	**206**	96	79[c]	*ent*-**206**	90	85[c]

[a] All reactions were performed at −55 °C for 60 h using 1.1 eq. of alkaloid and 3.0 eq. of benzyl alcohol in a toluene/CCl_4-mixture (1:1); for quinidine: 0.2 M with respect to the anhydride, for quinine: 0.05 M. [b] Determined by GC-analysis of the corresponding lactones using a chiral stationary phase. [c] After chromatographic purification (see experimental section).

Concerning the tricyclic anhydrides the results were even more positive. For example, both benzyl ester enantiomers derived from oxanorbornene anhydride **203** were formed in a highly enantioselective manner (Table 3, entry 3). In contrast, the corresponding methanolysis gave both stereoisomers with 18% ee difference. Also the yields of **204** and *ent*-**204** were significantly higher than those of products which

were obtained from the opening with methanol. This is probably due to a lower water solubility of the benzyl hemiesters, which results in a reduced loss of product during the aqueous workup. Since such oxatricyclic molecules are known to react with basic reagents,[203] the second extraction procedure was omitted and the products were purified by chromatography (entries 3 and 4).

The enantiomeric excesses of the benzyl esters were determined by GC-analysis of the corresponding lactones, which were obtained by selective reduction of the ester group with $LiBEt_3H$ followed by acid-catalyzed lactonization.[172b] Since the absolute configurations of the methanolysis products were already established,[180b] the retention times of the lactones derived from these methyl esters permitted a direct assignment also for the benzyl analogues. As expected, in all cases the stereochemical outcome of the desymmetrization was uniform: the quinidine-mediated ring opening of anhydrides generated the ester function at the carbonyl group indicated in Scheme 61.



Scheme 61: Stereoselective Desymmetrization of *meso*-Anhydrides with Benzyl Alcohol.

For the anhydrides containing unsubstituted all-carbon backbones, this is the *pro*-*S*-carbonyl group and, due to the reversal of the CIP-priorities, it is the *pro*-*R*-carbonyl group of anhydrides **172**, **203** and **205**. Analogously, pseudoenantiomeric quinine always showed the opposite selectivity. Due to the fact that this stereoselection rule is strictly valid for a wide range of substrates, the absolute configurations of other alcoholysis products become highly predictable.[180b]

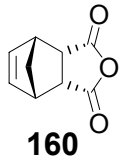
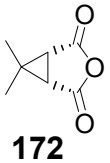
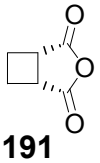
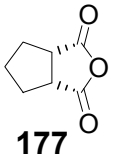
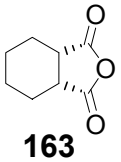
This newly developed methodology is of practical utility since a wide range of benzyl hemiesters are for the first time easily available in enantiomerically enriched forms. The protocol is also net superior to the enzymatic methods, since no enzyme has been shown to be able to hydrolyze benzyl diesters.

3.1.3 Investigation of the solvent system

In the methanolysis reaction, the highest enantiomeric excesses were achieved using a solvent system consisting of a 1:1 mixture of toluene and CCl_4.[180b] However, combinations of solvents without the potentially harmful halogenated solvent[204] were also applicable and gave products with high ee values.[180b]

In the course of the present study it was found that using benzyl alcohol as nucleophile, the anhydride openings occurred with almost the same enantioselectivities and yields in pure toluene; the fact that now the quinine-mediated alcoholysis requires less solvent differs from the previous observations. The largest difference in enantioselectivity between reactions performed in mixtures of toluene/CCl_4 (Table 2, entry 1) and pure toluene (Table 4, entry 2) was Δee = 3% for ester *ent*-**190**. In some cases, avoiding the use of CCl_4 led to even a slightly higher enantiomeric excess (Table 4, entries 3 and 5). These results stimulated and encouraged us to evaluate the performance of the ring opening reaction on a large scale.

Table 4: Opening of Various *meso*-Anhydrides in Toluene as Solvent[a]

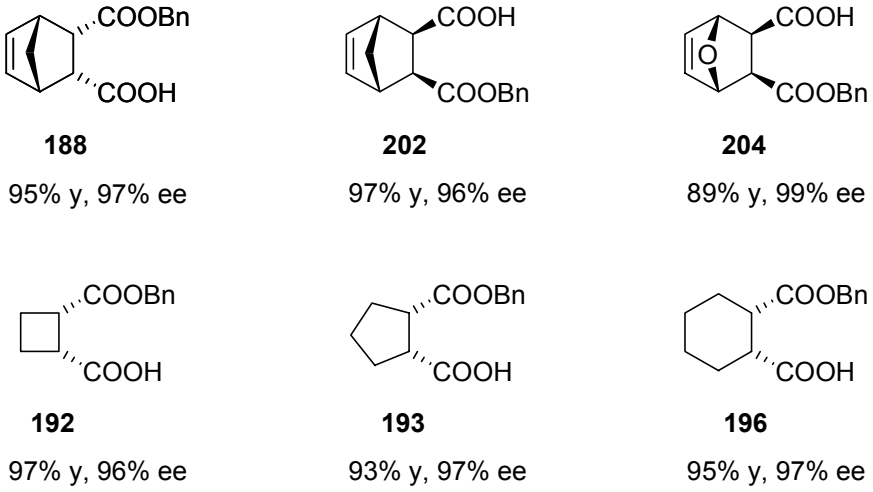
		Quinidine-Mediated			Quinine-Mediated		
Entry	Anhydride	Ester	ee (%)[b]	Yield (%)	Ester	ee (%)[b]	Yield (%)
1	 **160**	**188**	96	84	*ent*-**188**	95	90
2	 **172**	**190**	90	93	*ent*-**190**	85	86
3	 **191**	**192**	95	94	*ent*-**192**	90	90
4	 **177**	**193**	95	94	*ent*-**193**	94	90
5	 **163**	**196**	96	85	*ent*-**196**	93	86

[a] All reactions were performed at −55 °C for 60 h using 1.1 eq. of alkaloid and 3.0 eq. of benzyl alcohol in toluene as solvent; for quinidine: 0.2 M with respect to the anhydride, for quinine: 0.1 M. [b] Determined by GC-analysis of the corresponding lactones using a chiral stationary phase.

3.1.4 Reaction scale-up

With the norbornene anhydride as test substrate, we carried out the reactions in the presence of quinidine, respectively quinine, on a 20 mmol scale in pure toluene as solvent. Surprisingly, both enantiomers were isolated with 97% ee and in excellent yields (95% and 94%, respectively).[205] Guided by these results, we next selected

other representative substrates and evaluated them in the reaction with benzyl alcohol and quinidine as mediator. In all cases, the hemiesters were obtained in higher yields and greater enantioselectivities compared to the 1 mmol version. Remarkably, the oxanorbornene derivative **204** was isolated in 89% yield, after column chromatography, and >99% ee. This result is even more relevant when one consider that cleavage of the oxygen bridge offers easy access to carba-sugar derivatives.[203a] Investigations for the development of useful asymmetric syntheses, involving the alkaloid-mediated anhydride opening as a key step, are currently in progress.



Scheme 62: Quinidine-Mediated Ring Opening of Various *meso*-Anhydrides.

An advantage of the present protocol using benzyl alcohol as nucleophile, is that it allows the reactions to be performed in toluene as solvent, avoiding the use of the previously applied toxic carbon tetrachloride.

3.2 Synthesis of β-amino acids

Considerable attention has been drawn, in recent years, to the development of efficient strategies for the synthesis of optically pure β-amino acids[206] and especially cyclic ones.[207] The increasing interest in such cyclic β-amino acids is a result, on the one hand of the fact that many of these compounds show antibiotic, antifungal,

cytotoxic or other important biological properties in free form or as part of peptidic products.[202,207,208] On the other hand, Gellman's reports on oligopeptidic *trans*-2-aminocycloalkane carboxylic acid chains, which can fold into stable helical structures,[209] raised the demand of efficient synthetic routes to β-amino acid derivatives. Furthermore, cyclic β-amino acids are of considerable significance in synthetic organic chemistry for the preparation of pharmacologically active heterocyclic products.[207,210]

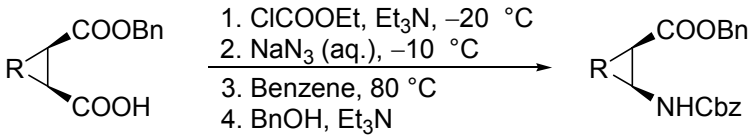
3.2.1 Preparation of *N*-Cbz protected amino acid benzyl esters

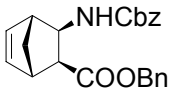
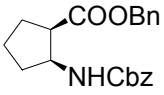
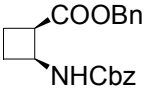
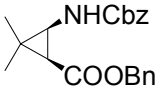
Representative benzyl monoesters were selected to demonstrate that they are valuable intermediates for the synthesis of highly enantiomerically enriched β-amino acids. For the synthesis of *N*-Cbz protected β-amino acid benzyl esters, the corresponding dicarboxylic monoesters were activated by treatment with ethyl chloroformate and triethylamine. Addition of an aqueous solution of sodium azide afforded crude acyl azides, which were dissolved in benzene and subjected to thermal rearrangement. After removal of the solvent, addition of benzyl alcohol to a methylene chloride solution of the resulting isocyanates in the presence of triethylamine gave the desired amino ester derivatives without purification of any of the intermediates.[181,200]

The results shown in Table 5 were obtained by performing the reactions on a 15 mmol laboratory scale. However, due to the ease of all the synthetic steps, and the accessibility of the substrates, larger quantities are easily manageable. The enantiomeric excesses of the products were determined by HPLC using columns with chiral stationary phases. Samples of racemic compounds were used as reference. Only in a single case, the conversion of hemiester **190**, we encountered difficulties. Presumably, they were due to the donor-acceptor substituted cyclopropane core of the corresponding β-amino acid which is prone to undergo rapid ring opening reactions.[211] Although the Curtius degradation has frequently been applied to such three-membered cyclic systems,[211e,212,213] **210** was only obtained with

a low ee (entry 4). It is most likely that this (partial) racemization proceeded *via* an open-chain intermediate which then underwent a stereospecific ring closure (as revealed by NMR spectroscopy).

Table 5: Preparation of *N*-Cbz-Protected β-Amino Acids

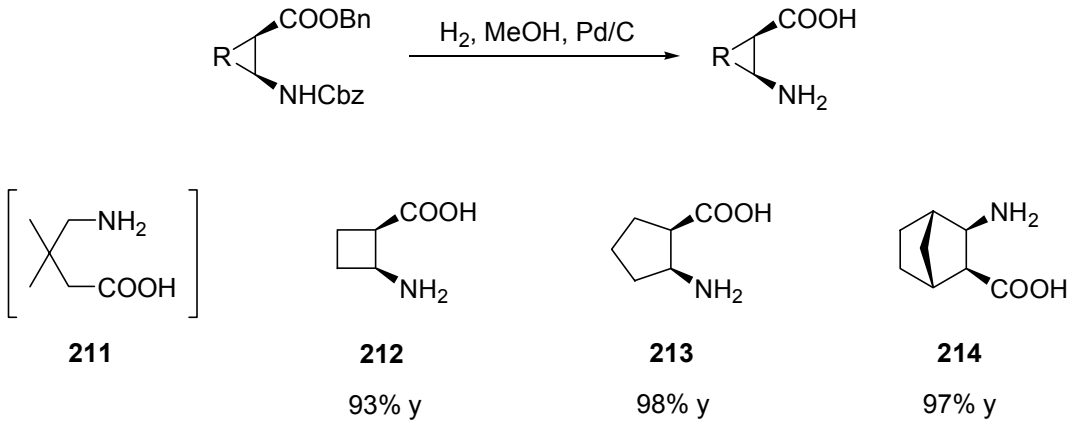


Entry	Mono-Benzyl Ester[a]		β-Amino Ester	ee (%)[b]	Yield (%)
1	**202**	(95% ee)	 **207**	93	72
2	*ent*-**193**	(94% ee)	 **208**	94[c]	77
3	*ent*-**192**	(93% ee)	 **209**	93	74
4	**190**	(92% ee)	 **210**	19	70

[a] The ee-values given in parentheses refer to the ones of the mono-benzyl esters obtained by the asymmetric opening of the corresponding anhydrides on a 15 mmol scale. [b] Determined by HPLC-analysis using a chiral stationary phase. [c] Recrystallization furnished an increase on >99.7% ee (HPLC-analysis).

3.2.2 Synthesis of the free β-amino acids

Finally, the ester and the carbamate protecting groups were removed in a single step by a simple hydrogenation delivering the free β-amino acids in excellent yields (Scheme 63). The Pd/C-catalyzed deprotection step, which was performed at 1 atm hydrogen, required a reaction time of 1-2 h for complete conversion (monitored by t.l.c.).



Scheme 63: Synthesis of Cyclic β-Amino Acids.

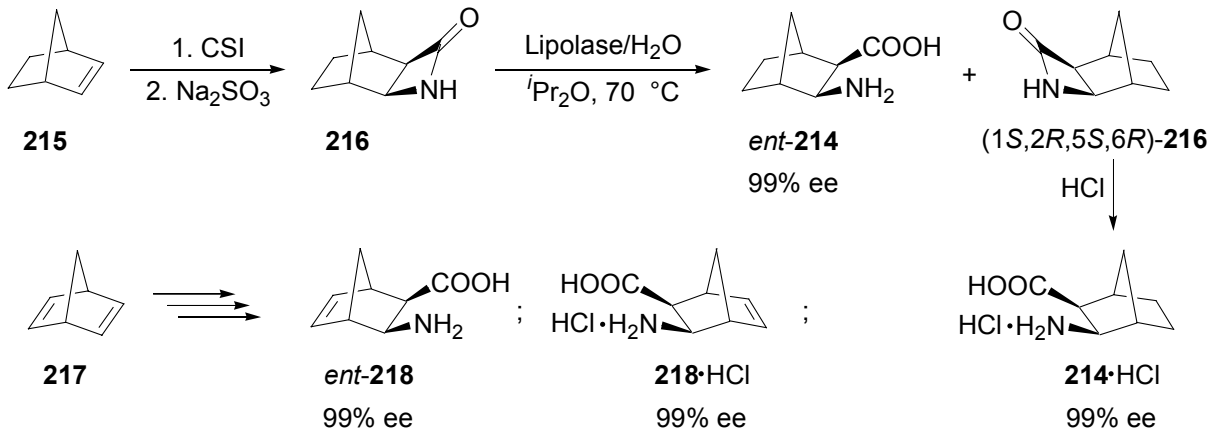
The instability of the three-membered ring also became apparent during the attempted hydrogenolytic deprotection of **210** to give the free amino acid. Even in the presence of HCl the desired product was not obtained and the only identified product (NMR spectroscopy) was the corresponding ring-opened achiral γ-amino acid **211**.

Along these lines, another interesting observation was made in the hydrogenolytic deprotection of **209**. In this case, the corresponding free amino acid **212** was obtained in high yield, when the hydrogenation was performed under standard conditions. However, extending the reaction time to 12 hours also led to C-C-bond cleavage. Hence, with this substrate, the deprotection is substantially faster than the ring-opening of the cycloalkyl backbone allowing to isolate the desired cyclobutane amino acid in high yield. In the first synthesis of optically active cyclobutane amino acid **212**, Ortuño and co-workers recently used the methyl ester analogue of *ent*-**192** as starting material, which was prepared by pig liver esterase-catalyzed

chemoselective hydrolysis of the corresponding *meso*-diester.[213,214] Subsequent Curtius rearrangement afforded the amino methyl ester equivalent to **209**, whose saponification required particularly mild reaction conditions due to its tendency to epimerize. Finally, hydrogenation led to the highly hygroscopic free amino acid **212** with 91% ee in 73% yield. It is worthy of note that the last two steps in Ortuño's approach gave products which were unsuitable for microanalysis so our synthetic route represents a considerable improvement in terms of product purity, enantioselectivity and yield as it provided analytically pure **212** in 93% yield and 93% ee. In this context, it should be also mentioned that the ee value of 93% was correlated with an optical rotation of $[\alpha]^{rt}_D = -80$ (*c* = 1.0, H_2O), a fact which is in contrast with Ortuño's findings where the ee value of 91% was correlated with $[\alpha]^{rt}_D = -9$ (*c* = 1.5, H_2O). However, recent studies from Aitken on the stability of the cyclobutane β-amino acid have shown that subjection of the *N*-Cbz protected β-amino acid to Ortuño's deprotection conditions resulted in a mixture of three amino acids, of which the least abundant one possesses NMR data identical with those of the expected product.[215] Recently, an alternative strategy which allowed the synthesis of both enantiomers with >97% ee has been described.[216] Furthermore, (−)-2-aminocyclobutane-1-carboxylic acid **212** has been used by Ortuño for the synthesis and structural investigation of conformationally constrained β-dipeptides.[214,217]

The application of this new protocol allowed the simplified asymmetric synthesis of cispentacin (**213**), an antifungal antibiotic which was independently isolated a decade ago by two Japanese groups from *Bacillus cereus* and *Streptomyces setonii*,[218] and was first prepared enantioselectively by Davies.[219] Recrystallization of **208** allowed to increase the ee to >99.7%. In our previous approach towards cispentacin, which involved the *meso*-anhydride opening with methanol as nucleophile, epimerization of the amino ester during its saponification was observed. Consequently, a mixture of diastereomeric products was obtained.[181a] This problem was solved by employing an acidic hydrolysis which yielded the hydrochloric salt of the fungicide. However, in this case an additionally ion exchange chromatography was required to liberate the unprotected amino acid.

While carbon-carbon double bonds in substrates with a cyclohexene backbone do not react under these conditions,[220] hydrogenation of norbornene amino ester **207** delivered the saturated amino acid **214**. Although quite expensive, racemic **214**[221] is commercially available and was recently used in a Ugi four-center, three-component reaction to produce the appropriate β-lactams.[222] In addition, a simple and efficient direct method for the synthesis of both enantiomers has been developed by Fülöp.[223] Herein, 1,2-dipolar cycloaddition of chlorosulfonyl isocyanate (CSI) to the (bicyclo[2.2.1]hept-2-ene) norbornene afforded racemic exo-3-azatricyclo[4.2.1.$0^{2,5}$]nonan-4-one. Enzyme catalyzed enantioselective ring opening of the racemic β-lactam ($\pm$)-**216** yielded the enantiomerically enriched amino acid *ent*-**214** and the lactam (1*S*,2*R*,5*S*,6*R*)-**216**. Treatment of the lactam (1*S*,2*R*,5*S*,6*R*)-**216** with 18% HCl furnished enantiopure **214**. Furthermore, the unsaturated analogs are also available from norbornadiene by following a similar reaction sequence.



Scheme 64: Amino Acids Synthesis According to Fülöp.

3.3 Chiral bisoxazolines

Over the last few years, C_2-symmetric chiral bisoxazolines have proved to be an efficient class of ligands in a large variety of asymmetric transformations and several general methods are now available for their synthesis.[224] C_3- and pseudo C_3-

symmetric trisoxazolines have also been designed and successfully applied in asymmetric catalysis.[225]

Due to their great potential which was proved in the initial applications, much effort has been devoted to the modification of the bisoxazoline framework in order to achieve superior ligands. The conformationally constrained metal chelate and the presence of stereocenters close to the nitrogen donor atoms assure a well ordered chiral environment at the catalytic site. Generally, the chirality in these ligands is derived from the optically active β-amino alcohols employed for the oxazoline ring formation. Since a large variety of optically pure amino alcohols are easily accessible either by simple reduction of the corresponding α-amino acids, or by means of asymmetric synthesis employing chiral auxiliaries, the ligand optimization with respect to variation of the oxazoline groups encountered no problems so far. The size of the chelate also proved to be important since it controls the orientation of the substituents around the metal centre. Beside this, the number of possible transition states in a particular reaction is minimized by the presence of a C_2-symmetry axis in the chiral ligand. Among all known C_2-symmetric bisoxazolines, the most widely used ones are those forming five- and six-membered metal chelates. In contrast, the development and application of seven-membered chelate systems is still limited. Recently, a new class of 1,4-bisoxazolines with a rigid, chiral, cyclic 1,3-dioxolane backbone was introduced and optimized by Andersson for the asymmetric copper-catalyzed cyclopropanation of olefins.[226] Two sets of diastereomeric ligands were readily available from L-amino acids and either L- or D- tartaric acid. The effect of both, different oxazolinyl groups and different substituents on the dioxolane ring, on the reaction diastereo- and enantioselectivity has been carefully investigated. In the same context, Knight carried out a direct comparison of the level and sense of asymmetric induction in the cyclopropanation and aziridination of styrene.[227] Independently, Ikeda has design such ligands for the rhodium(I) catalyzed hydrosilylation of acetophenone.[228]

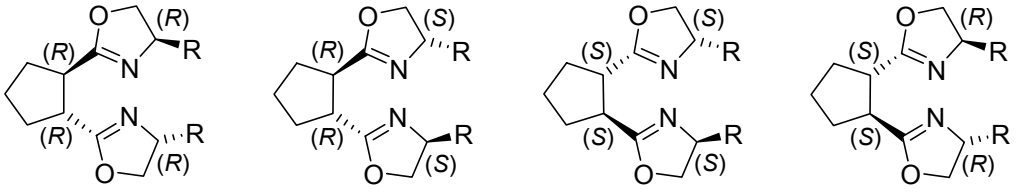
C_2-symmetric bisoxazolines, bearing a bicyclic chiral backbone, have been developed and introduced by Takacs for the room temperature enantioselective Diels-Alder reaction.[229] For this purpose, enantiomerically pure bicyclo[2.2.1]hept-5-ene-(2*S*,3*S*)-*trans*-dicarboxylic acid was synthesized by saponification of the diester

obtained in the Diels-Alder reaction between cyclopentadiene and L-menthol-derived dimenthyl fumarate. Coupling of the diacid with (*S*)-phenylglycinol and subsequent cyclization afforded the 1,4-box ligand containing all four stereogenic centers of (*S*) absolute configuration. Since the (2*R*,3*R*)-diacid is also available in optically pure form from the same approach, coupling with (*S*)-phenylglycinol led to a second, diastereomeric ligand.

In a similar fashion, chiral box ligands based on a *trans*-1,2-cyclohexane skeleton were developed and evaluated together with a series of common ligands in the palladium(II) asymmetric cyclization-carbonylation of 2-propargyl-1,3-dione.[230]

3.3.1 C_2-symmetric chiral bisoxazolines

In chapter 1.4.3 we demonstrated that our desymmetrization methodology offers easy access to enantiomerically enriched *cis*-1,2-dicarboxylic methylmonoesters.[180] Consequently the *trans* hemiesters and the corresponding diacids are also available in optically active form.[182,183] This led us to the idea of taking advantage of the organocatalytic asymmetric ring opening of *cis*-cyclopentanedicarboxylic anhydride, which would allow us to synthesize novel box ligands with a rigid, chiral, cyclic backbone. While designing these compounds, we had in mind several structural features which would make them effective in the metal-catalyzed reactions.

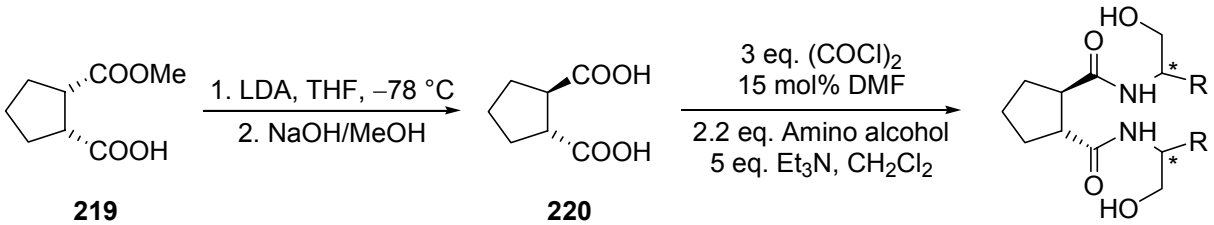


Scheme 65: Possible Cyclopentane Derivatives.

Firstly, they possess four stereogenic centers, two from the chiral backbone and two from the amino alcohol (Scheme 65). The presence of stereogenic centers on the backbone in addition to those on the oxazoline rings introduces an extra element of complexity in the ligand structure. Since both enantiomers of the diacid are readily

available from the desymmetrization reaction, the stereochemistry of the four asymmetric centers is easily adjustable, giving us the possibility to investigate and compare their effect on the ligand activity. Secondly, the bulkiness of the substituent on the oxazoline ring is adjustable by simply changing the amino alcohol so the best ligand structure for a particular reaction can be obtained by appropriate selection of stereochemistry and bulkiness of the substituent on the oxazoline ring.

Our synthetic route started with the quinidine mediated methanolysis of *cis*-cyclopentanedicarboxylic anhydride which afforded the corresponding methyl hemiester **219** in very good yield (95%) and high enantioselectivity (96% ee). Selective epimerization[184,231] and saponification provided the corresponding *trans* (1*R*,2*R*)-diacid **220** in 78% yield. Activation of the acid functions and subsequent coupling with an optically pure amino alcohol yielded the desired C_2-symmetric dihydroxy diamide (Scheme 66). The Vilsmeier reagent, chloromethylene dimethylammonium chloride, generated *in situ* from DMF and oxalyl chloride, was employed as activating reagent. Conversion of the diacid into the corresponding acid dichloride was accomplished within one hour, the solvent and the excess oxalyl chloride were removed in high vacuum delivering the product which was used in the next step without further purification. Overnight reaction with 2.2 eq. amino alcohol and triethylamine afforded the expected bis hydroxyamide as a white solid which was insoluble in methylenchloride. All attempts to purify the crude product by an aqueous work up therefore failed and the bisamide was isolated in optically and analytically pure form by simple filtration and washing with methylenchloride. The NMR-analysis confirmed the presence of the desired product as a single diastereomer.



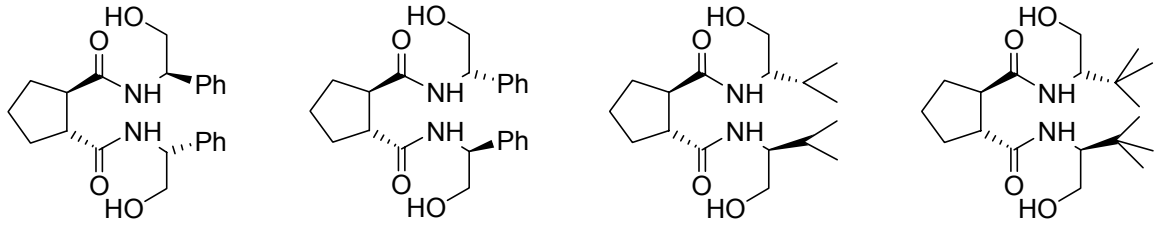
219
96% ee

220
78% y

R = Ph, ^{t}Bu, ^{i}Pr.

Scheme 66: Synthesis of bis-Hydroxyamides from Hemiester **219**.

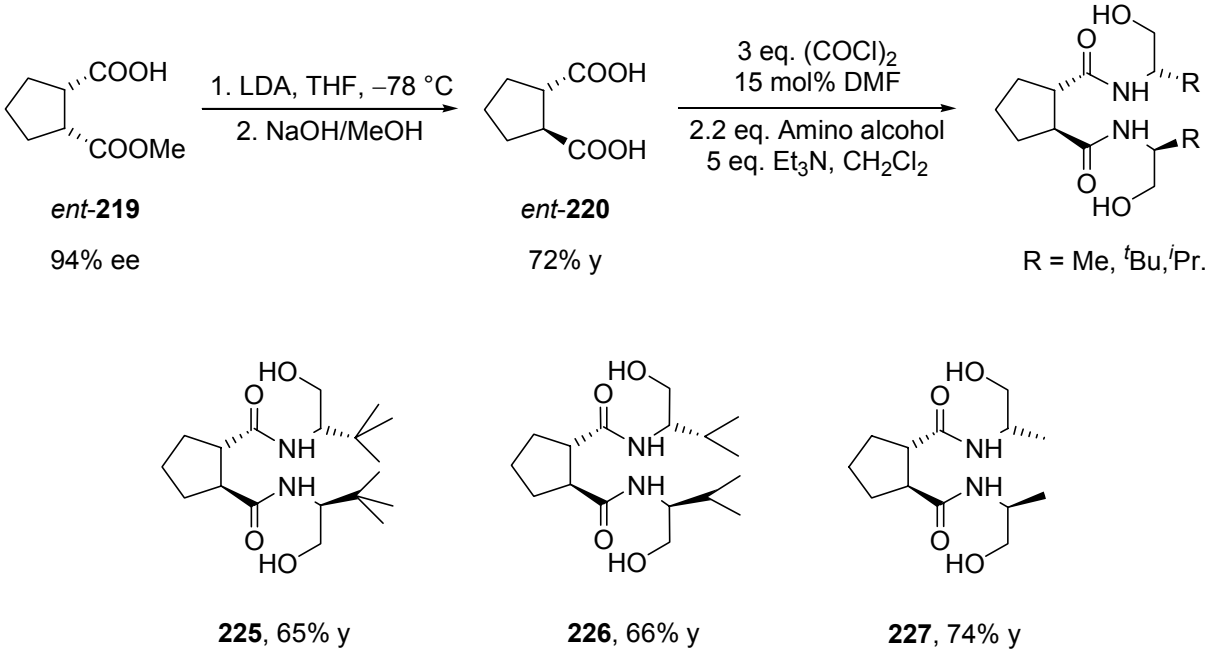
Following this general reaction scheme, four derivatives were readily available in good yields starting from the diacid **220**. Reaction with *R*- and *S*-phenylglycinol, respectively, afforded the products **221** and **222** as a pair of two diastereomers.



221, 62% y **222**, 70% y **223**, 70% y **224**, 62% y

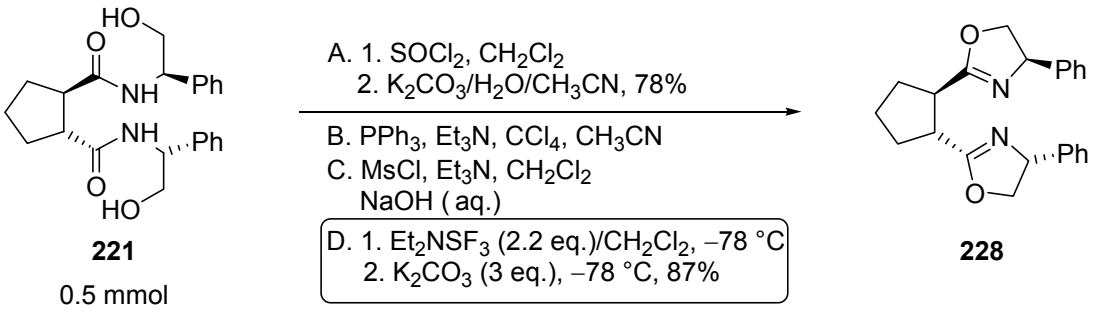
Scheme 67: C_2-Symmetric Dihydroxy Diamides.

The isopropyl and *tert*-butyl analogs of **222**, derived from amino alcohols of *S*-absolute configuration, were synthesized in order to investigate the effect of different substituents on the ligand activity. Since examination of the effect of their different orientations around the metal site was desirable, amino alcohols of *R* configuration were next required. Taking in consideration the high cost of *R*-*tert*-leucine, and consequently *R*-*tert*-leucinol, we decided, as an alternative, to synthesize the corresponding enantiomer by using the *trans* (1*S*,2*S*)-diacid *ent*-**220** as precursor and *S*-*tert*-leucinol as coupling partner and leading to the bisoxazoline containing all four stereogenic centers of (*S*) absolute configuration. For this purpose, the enantioselective methanolysis was carried out in the presence of quinine, affording the hemiester *ent*-**219**. Selective epimerization and saponification provided the corresponding *trans* (1*S*, 2*S*)-diacid *ent*-**220** in 72% yield. The subsequent activation and coupling steps were carried out in the same manner as described above. Accordingly three derivatives were readily available in good yields starting from *ent*-**220** (Scheme 68).



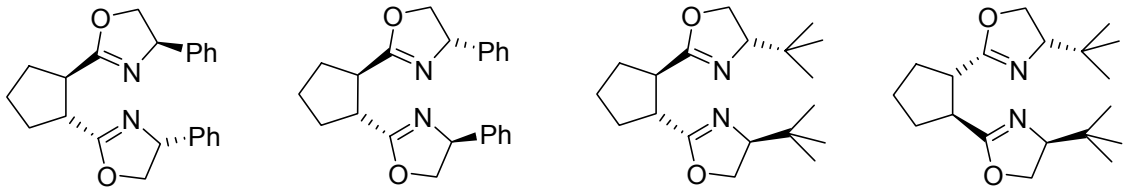
Scheme 68: Synthesis of bis-Hydroxyamides from Hemiester *ent*-**219**.

With the (*R*)-phenylglycinol derivative **221** as model substrate the conditions for the oxazolin ring closure were optimized (Scheme 69). Activation with thionyl chloride, treatment with base and purification afforded the product in 78% yield. Surprisingly, no product could be detected under Appel conditions (PPh_3, Et_3N, CCl_4, MeCN). Unsatisfactory yield was observed when the bisamide was treated with mesyl chloride to give the corresponding bismesylate followed by heating to reflux in an aqueous methanolic NaOH solution. However, activation with diethyl amino sulfur trifluoride at −78 °C in methylenechloride[232] followed by base induced cyclization and purification by column chromatography afforded the desired product in 87% yield. We therefore decided to apply this set of conditions to all substrates.



Scheme 69: Selected Methods for the Oxazolin Ring Closure.

Accordingly, four derivatives were isolated in high yields, in optically and analytically pure form (Scheme 70). To our surprise, **227** did not cyclize under these mild conditions and **223** gave a crude mixture which was not suitable for purification by column chromatography. Alternative routes for their cyclization and purification are currently being researched.



228, 90% y
L_1

229, 80% y
L_2

230, 92% y
L_3

231, 83% y
L_4

Scheme 70: C_2-Symmetric Bisoxazolines.

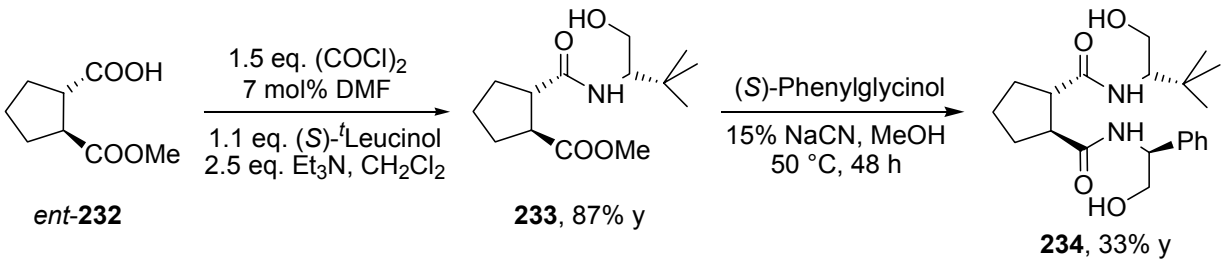
3.3.2 C_1-symmetric chiral bisoxazolines

The presence of an acid and an ester functional group in the same molecule allows a sequential functionalization. We therefore investigated the possibility of a stepwise introduction of two different amino alcohols in the same molecule. This would permit the synthesis of C_1-symmetric chiral bisoxazolines and demonstrate whether a C_2-symmetric ligand is essential for achieving high levels of diastereo- and enantiocontrol for a specific reaction (in the case of a C_1-symmetric ligand the situation is more complex since the number of possible TS is double).

There are only two examples in the literature for the synthesis of asymmetric bisoxazolines.[233] Early work from Nishiyama describes the synthesis of an asymmetric bisoxazoline ligand by a stepwise introduction of two different amino alcohols on an achiral backbone.[233a] The first coupling step in the sequence made use of dimethyl pyridine-2,6-dicarboxylate and 2-aminoethanol, leading to the corresponding achiral monoamide methyl ester. A chiral amino alcohol was employed in the second step, to give after cyclization, the so-called “single chiral” pybox type ligand. The resulting

ligands were evaluated in the ruthenium-catalyzed cyclopropanation of styrene with various alkyl diazoacetate and enantioselectivities with up to 94% ee were obtained for the *trans* cyclopropane. More recently, Guiry described the synthesis of a new class of tridentate bisoxazoline ligands by a four-step convergent synthesis, employing a Hartwig-Buchwald type Pd-catalyzed aryl amination as a key step.[233b]

Our present approach should allow the introduction of two different chiral amino alcohols on the same chiral backbone. In order to validate our design we first synthesized the mono amido ester derivative **233** and examined the possibility of introducing a second, different amino alcohol into this molecule. Cyanide catalyzed trans amidation[234] afforded the desired mixed bisamide **234** in only 33% yield after chromatographic purification.



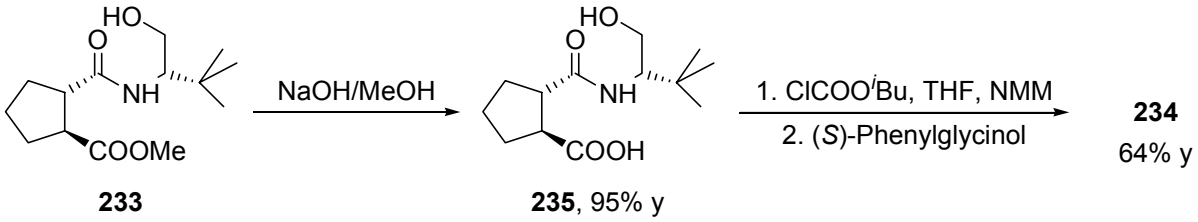
ent-**232** **233**, 87% y **234**, 33% y

Scheme 71: Synthesis of mixed-Dihydroxydiamide **234** from *trans* Hemiester ent-**232**.

Due to the low yield obtained, even after extended reaction time, we decided to focus on alternative protocols which may allow an increase in the reaction yield. Hence, the amido ester **233** was converted into the corresponding mono amido acid derivative **235**. The saponification was completed within four hours (t.l.c. controlled) and the reaction mixture was acidified and extracted with methylenchloride. Evaporation of the solvent and drying in high vacuum afforded the product in 95% yield in analytically pure form.

The presence of a free OH group in the molecule excluded the use of activating reagents such as thionyl and oxalyl chloride, so use of the mixed anhydride formation as activating method was chosen. Activation with isobutyl chloroformate in THF and reaction with (*S*)-phenylglycinol afforded the desired product in 64% yield after

chromatographic purification. In comparison with our first approach, the result was promising but still not satisfactory, so alternative coupling reagents were investigated.

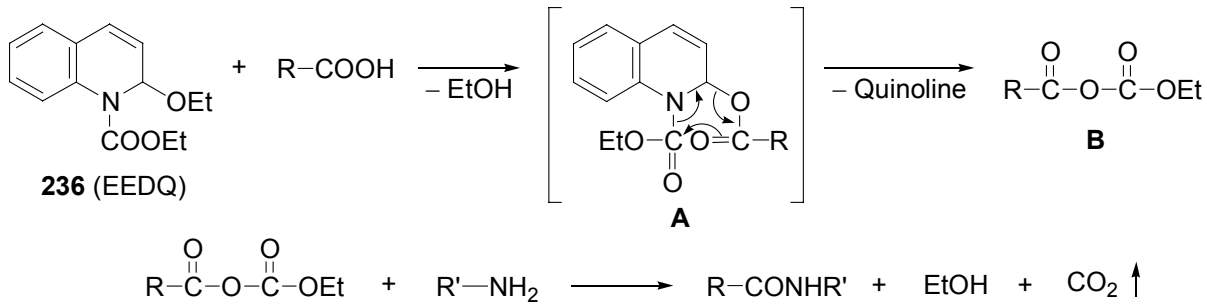


233 **235**, 95% y

Scheme 72: Synthesis of mixed-Dihydroxydiamide **234** from **233**.

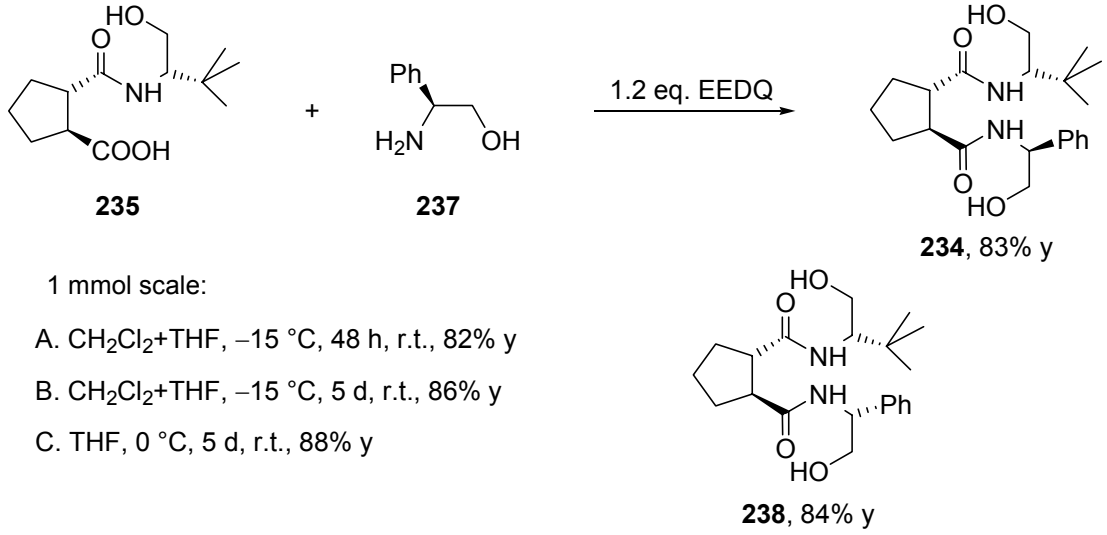
Typical coupling reagents such as DCC and EDCI were excluded due to the potential problems which could encounter during the purification process. Highly reactive DCC is the most widely used reagent for amide bond formation and usually gives good yields within short reaction times. However, since the dicyclohexylurea byproduct is almost insoluble in most organic solvents used for coupling reactions and taking into account the above mentioned product solubility problem (the bis amide proved to be insoluble in both water and most of the organic solvents) difficulties in product purification were envisaged. Water-soluble derivatives such as 1-ethyl-3-(3'-dimethylaminopropyl)carbodiimide hydrochloride (EDCI), were also eliminated since the purification would require an aqueous extraction in order to remove the urea byproduct.

Initially developed as a depressor for the central nervous system,[235] 1-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline (**236**) (EEDQ) also proved to be an efficient and selective coupling reagent for the formation of peptide bonds.[236] With the aid of EEDQ, the carboxylic acid is converted *via* intermediate **A** into the highly active mixed anhydride **B**, which reacts with an amino acid (or peptide ester) to form the peptide. The byproducts obtained in the reaction are quinoline, ethanol and CO_2, all easily removable. It was also proved that no racemization occurred during this process and that the formation of **A** is slow, while its consumption by the nucleophile is very fast. The great advantage of EEDQ as coupling reagent is that hydroxy amino acids do not require side-chain protection under these reaction conditions.



Scheme 73: EEDQ as Coupling Reagent.

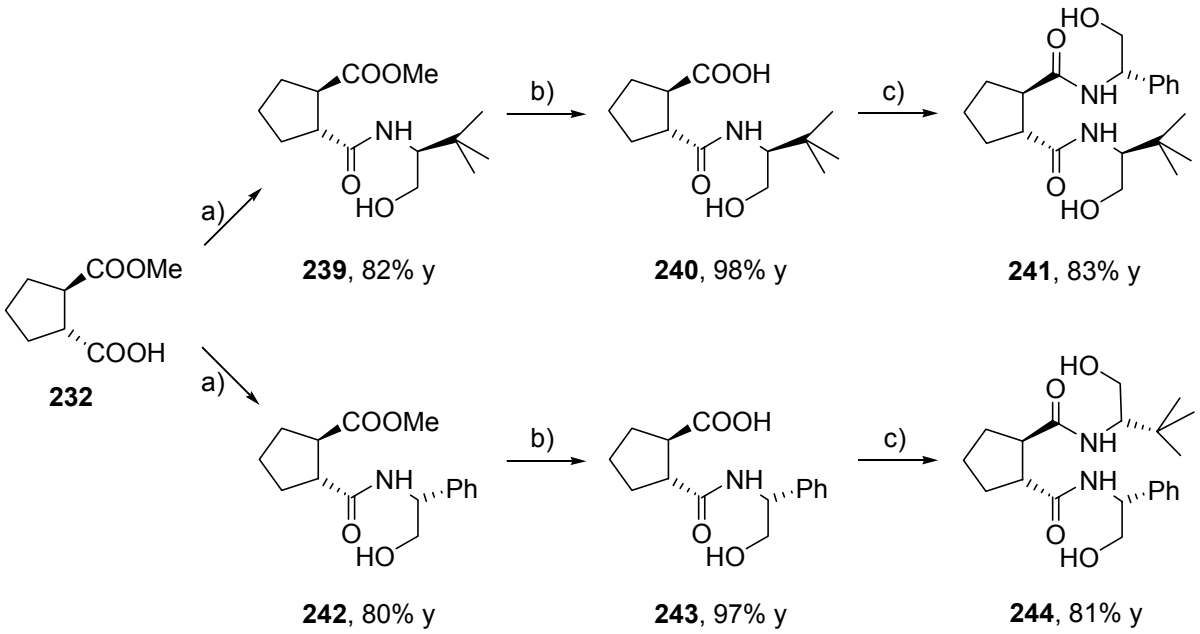
Taking in consideration the advantages of the above protocol, we decided to apply it in test on our substrates under different reaction conditions. Initially, the reactions were carried out on a 1 mmol scale and the results are summarized in Scheme 73. In a first approach (*S*)-phenylglycinol was added, as a methylenechloride solution, to the precooled solution (0 °C) of the hydroxy amido acid (CH_2Cl_2 + 20% THF). The mixture was then cooled to −15 °C and a solution of EEDQ was added *via* syringe. The reaction was stirred at r.t. for 48 h, the solvent and ethanol byproduct were removed in vacuum and the crude mixture was purified by column chromatography, yielding the desired product in 82% yield in analytically and diastereomerically pure form. Extention of the reaction time to 120 h resulted in a slight increase in the reaction yield (86 vs. 82%). In a third approach, the EEDQ was added as a solid to a cooled solution (0 °C) of the two reactants in THF. The mixture was allowed to warm to r.t. and stirred for 120 h. The product was purified as previously described and isolated in 88% yield. After this preliminary investigation, the latter version seemed to be more suitable since the reaction was easier to perform compared to the first approaches.



Scheme 74: Alternative Synthesis of mixed-Dihydroxydiamides **234** and **238** from **233**.

Furthermore, the reaction scale-up was achieved without any problems, so that **234** was isolated in good yield (83%) on a 7 mmol scale. In the same manner, reaction of **235** with (*R*)-phenylglycinol afforded the corresponding mixed bis-amide **238** in 84% yield. Since the two amino alcohols are available in both enantiomeric forms, it should be possible to synthesize all four oxazoline combinations of a potential ligand with the same chiral backbone.

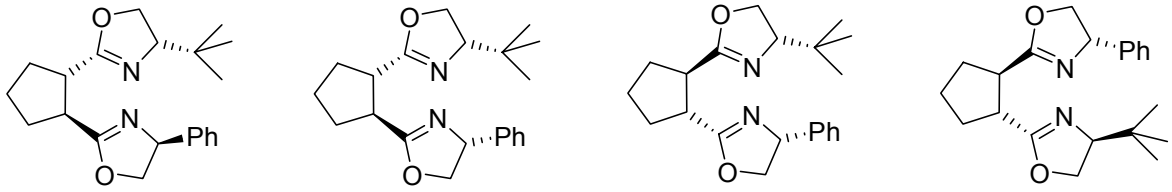
Since a comparative study on the effect of these two different oxazolinyl substituents on the ligand activity and selectivity was desired, our next targets were the two remaining bis-amides precursors. Again, in order to avoid the use of expensive (*R*)-*tert*-leucinol, our attention was drawn to the preparation of the corresponding enantiomeric ligands which required the opposite stereochemistry in the substrates. For this purpose, the same methodology was successfully applied on the hemiester obtained from the quinidine mediated methanolysis of *cis*-cyclopentanedicarboxylic anhydride, affording in the end the two mixed dihydroxy diamides **241** and **244** in good overall yields (Scheme 75).



a) (1) 1.5 eq. $(COCl)_2$, 7 mol% DMF; (2) 1.1 eq. Amino alcohol, 2.5 eq. Et_3N, CH_2Cl_2
b) 3 eq. NaOH/MeOH; c) 1 eq. Amino alcohol, 1.2 eq. EEDQ, THF

Scheme 75: Synthesis of mixed-Dihydroxydiamides from *trans* Hemiester **232**.

Cyclization of these four mixed derivatives under the previously described protocol (activation with DAST and subsequent base induced ring closure) afforded the corresponding C_1-symmetric bisoxazolines in high yields (Scheme 76).

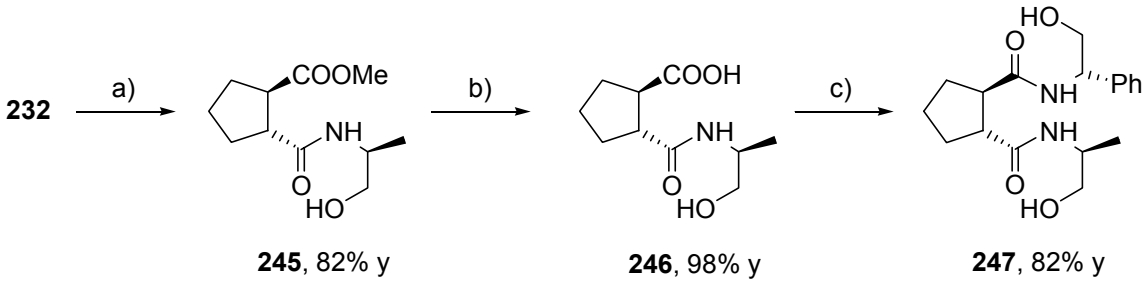


245, 83% y **L$_5$** | **246**, 81% y **L$_6$** | **247**, 84% y **L$_7$** | **248**, 84% y **L$_8$**

Scheme 76: C_1-Symmetric Bisoxazolines.

On the one hand these four mixed bisoxazolines offer us the possibility of studying the effect induced by a combination between phenyl as substituent on one oxazoline ring and the bulky *tert*-butyl group on the other one. On the other hand the effect induced by their different orientation around the metal site is also easy to follow.

Compound **247** (Scheme 77) was synthesized in order to study the influence of a less bulky group in combination with phenyl on the ligand activity. Unlike all our previous mixed substrates, **247** could not be cyclized under the same conditions and only traces of the starting material were isolated at the end of the reaction.



245, 82% y **246**, 98% y **247**, 82% y

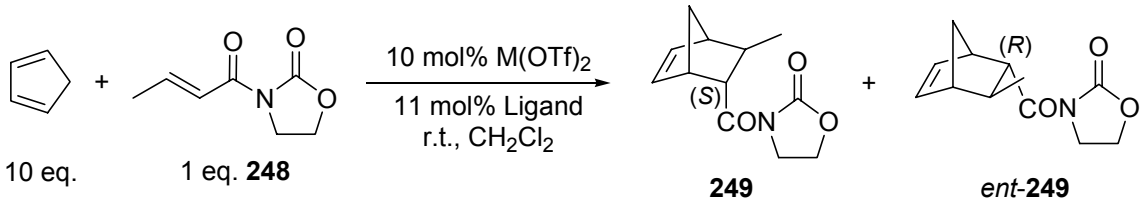
a) (1) 1.5 eq. $(COCl)_2$, 7 mol% DMF; (2) 1.1 eq. Amino alcohol, 2.5 eq. Et_3N, CH_2Cl_2
b) 3 eq. NaOH/MeOH; c) 1 eq. Amino alcohol, 1.2 eq. EEDQ, THF

Scheme 77: Synthesis of mixed-Dihydroxydiamide **247** from *trans* Hemiester **232**.

3.3.3 Application in catalysis

The enantioselective Diels-Alder reaction[229,237] was chosen as the first catalytic test reaction in order to determine the efficiency of the new ligand system. The results of the room temperature [M(box)]-$(OTf)_2$ catalyzed Diels-Alder reaction between *N*-acryloyl oxazolidinone **248** and cyclopentadiene are summarized in Table 6.

Table 6: Influence of Ligand Structure on the Enantioselective Diels-Alder Reaction.



10 eq. 1 eq. **248** **249** *ent*-**249**

Ligand	$Cu(OTf)_2$ (12 h)			$Zn(OTf)_2$ (36 h)		
	endo:*exo*[a]	ee[b] (%)	Yield (%)	*endo*:*exo*[a]	ee[b] (%)	Yield (%)
L_1	52:48	11[c]	93	85:15	38[c]	36
L_2	**77:23**	**71**	**96**	**85:15**	**71**	**99**
L_3	–	–	–	–	–	–
L_4	–	–	–	–	–	–
L_5	62:38	16	93	86:14	10	33
L_6	66:34	23	91	78:22	0	33
L_7	73:27	17[c]	98	81:19	55[c]	99
L_8	–	–	–	–	–	–

[a] *Endo*:*exo* ratios were determined by HPLC-analysis and confirmed by NMR.

[b] Determined by HPLC-analysis using a chiral stationary phase.

[c] Opposite enantiomer.

The catalysts were prepared by stirring a solution of the corresponding ligand (11 mol%) with the respective metal triflate, $M(OTf)_2$ (10 mol%) in CH_2Cl_2 at r.t., under argon, for 2-3 h. In the case of copper triflate the time was adjusted by checking the solution for the presence of colorless, undissolved triflate salt and by the formation, in all cases, of a clear, green or blue solution. At this stage the dienophile (0.25 mmol) was added, followed by freshly distilled cyclopentadiene (10 eq.).

In all cases the copper complexes exhibited faster reaction rates, affording the products in over 90% yield within 12 h whereas the zinc complexes required longer

reaction times, affording products in satisfactory yield in only two cases. On the other hand zinc complexes showed a better *endo*:*exo* selectivity compared with the copper analogs.

Ligand **L_2**, leads to a complex in which the two phenyl substituents are pointing toward the metal site and gives the best results in both copper and zinc catalyzed Diels-Alder reaction, namely affording the *endo* product with moderate diastereoselectivity and 71% ee. A substantial enhancement in the diastereoselectivity (70 vs 54% de) was observed when the zinc complex was employed in the reaction. In contrast, the diastereomeric ligand, **L_1**, showed only a low level of asymmetric induction, affording the product with opposite absolute configuration.

In the case of **L_3** and **L_4** the product was detected in only trace amounts, even if the reaction time was extended to several days. Since $Cu(OTf)_2$ itself is insoluble in methylene chloride and since a clear solution was obtained by mixing it with the ligand (**L_3** and **L_4**, respectively), we assume that copper coordinated to both nitrogen atoms, but the presence of the two bulky *tert*-butyl group did not offer sufficient space for the dienophile to approach the metal centre. This is also the case for the mixed ligand **L_8** where the two oxazolinyl groups are pointing toward the metal centre. If we compare the structure of our best ligand **L_2** with the one of ligand **L_8**, it is obvious that the only difference between them is the presence of the bulky *tert*-butyl group instead of the planar phenyl group on one oxazoline ring. This slight modification in the ligand structure causes finally the change from an active complex into an inactive one. In the remaining three mixed ligands, at least one substituent points away from the metal site so that the approach of the dienophile is less hindered compared with **L_8**. Among them, the metal complex derived from **L_7** showed the opposite sense of asymmetric induction.

The copper complexes derived from the five ligands which showed low to moderate activity in the r.t. catalyzed Diels-Alder reaction were next tested in the reaction at 0 °C. As can be seen in Table 7, the reaction time had to be extended from 12 h to 5

days to achieve good yields. Generally, the reaction at 0 °C afforded the *endo* products with slightly higher enantiomeric excesses.

Table 7: Effect of Temperature on the Diels-Alder Reaction.

Ligand	$Cu(OTf)_2$ (5 d)		
	endo:*exo*[a]	ee[b] (%)	Yield (%)
L_1	51:49	23	81
L_2	83:17	75	99
L_5	60:40	40	81
L_6	70:30	16	72
L_7	82:18	42[c]	80

[a] *Endo*:*exo* ratios were determined by HPLC-analysis and confirmed by NMR.

[b] Determined by HPLC-analysis using a chiral stationary phase.

[c] Opposite enantiomer.

Next the effect of the counterion on the catalyst activity was investigated. Thus, with the bisoxazoline **229** as chiral ligand, different copper sources were tested and it was observed that the yield and the *endo*:*exo* ratio remained essentially unaffected whereas the ee of the *endo* product dropped down (Table 8).

Table 8: Effect of the Counterion on the Reaction Selectivity.

Copper salt	*endo*:*exo*[a]	ee[b] (%)	Yield (%)
$Cu(OTf)_2$	77:23	71	96
$Cu(SbF_6)_2$	81:19	54	99
$Cu(ClO_4)_2$	75:25	46	99

[a] *Endo*:*exo* ratios were determined by HPLC-analysis and confirmed by NMR.

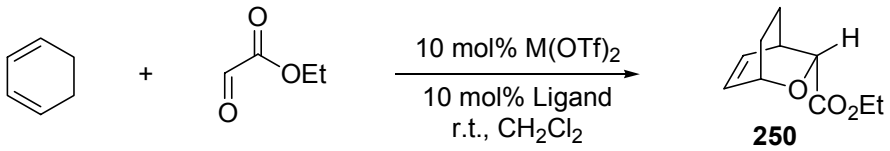
[b] Determined by HPLC-analysis using a chiral stationary phase.

Subsequently, the related hetero Diels-Alder reaction was investigated,[238] taking 1,3-cyclohexadiene and ethyl glyoxalate as test substrates. The chiral metal catalyst was prepared by mixing equimolar amounts of $Cu(OTf)_2$ (10 mol%) with the respective bisoxazoline ligand (10 mol%) in methylenechloride at r.t. for approximately 2 h. At this stage, freshly distilled ethyl glyoxalate was added, followed by 1,3-

cyclohexadiene and the reaction was stirred for 14 h. The results are summarized in Table 9.

The [Cu(box)]-$(OTf)_2$ catalyzed reaction of 1,3-cyclohexadiene and ethyl glyoxalate provided the HDA-adduct with high diastereoselectivities (>97% *endo* product) but in moderate yields and with low enantioselectivities (30-49% ee as determined by GC-analysis). It should be noted that the complex derived from ligand $\mathbf{L_7}$ resulted in the opposite enantioselectivity.

Table 9: Copper Catalyzed Hetero Diels-Alder Reaction.



250

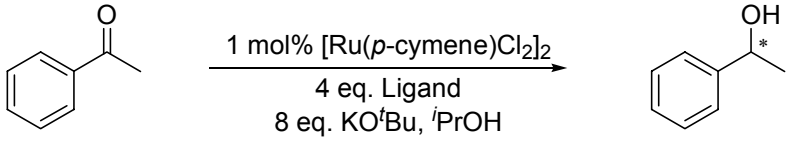
Ligand	$Cu(OTf)_2$ (14 h)		
	endo:*exo*[a]	ee[a] (%)	Yield (%)
L_1	97:3	39	65
L_2	97:3	49	68
L_3	–	–	–
L_4	–	–	–
L_5	97:3	45	70
L_6	98:2	30	50
L_7	98:2	37[b]	55
L_8	–	–	–

[a] Determined by GC-analysis using a chiral chiral stationary phase.

[b] Opposite enantiomer.

The catalytic behavior of the ruthenium complexes derived from our ligands was next investigated in the asymmetric transfer hydrogenation of acetophenone.[239] In all cases the catalytic system gave only low enantioselectivities (22-26% ee).

Table 10: Ruthenium Catalyzed Transfer Hydrogenation.



Ligand	[Ru(*p*-cymene)Cl_2]$_2$ (10 h)		Ligand	[Ru(*p*-cymene)Cl_2]$_2$ (10 h)	
	ee[a] (%)	Conv. (%)		ee[a] (%)	Conv. (%)
L_1	26 (*R*)	73	L_5	24 (*S*)	77
L_2	24 (*S*)	97	L_6	22 (*R*)	51
L_3	0	26	L_7	26 (*R*)	90

[a] Determined by GC-analysis using a chiral chiral stationary phase.

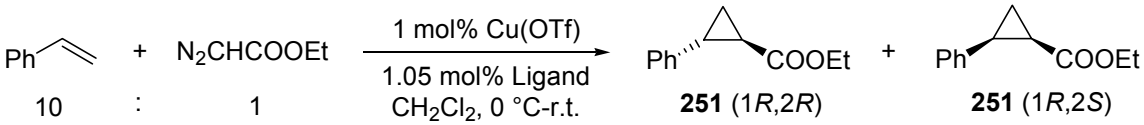
The enantioselective cyclopropanation of olefins is an area of current interest.[104,240] A major advance in this field was achieved by Pfaltz, who demonstrated that the Cu(I) complexes derived from C_2-symmetric chiral semicorrins are useful catalysts for the enantioselective cyclopropanation of olefins with diazo compounds.[241] Subsequently, copper and ruthenium-box complexes emerged as efficient catalysts for the enantioselective cyclopropanation reaction.[242] Recent reports from Andersson on comparative studies on the effect of the chelate ring size on the ligand activity[226] encouraged us to evaluate our set of ligands in the intermolecular cyclopropanation reaction.

In a preliminary study, styrene and ethyl diazoacetate were chosen as standard substrates in order to determine the efficiency of our ligand system. The cyclopropanation was carried out in the presence of 1 mol% CuOTf and 1.05 mol% of chiral ligand in dry methylenechloride. The optimum complexation time was established to one hour. Then, the catalyst solution was cooled to 0 °C, styrene was added, followed by slow addition of the ethyl diazoacetate solution (in methylenechloride) over 5 h *via* syringe pump. The reaction was stirred overnight at r.t. and the results are summarized in Table 11.

All four mixed ligands showed low or no asymmetric induction. The two diastereomeric C_2-symmetric ligands bearing phenyl groups on the oxazoline rings

exhibited slightly higher levels of asymmetric induction (but still insufficient) compared to the mixed ones, affording the *trans* products with 36 and 35% ee, respectively.

Table 11: Enantioselective Cyclopropanation of Styrene.



251 (1*R*,2*R*) **251** (1*R*,2*S*)

Ligand	*trans*:*cis*[a]	ee[b] (*trans*) (%)	ee[c] (*cis*) (%)	Yield (%)
L_1	72:28	36 (1*S*,2*S*)[d]	26(1*S*,2*R*)	65
L_2	72:28	35 (1*R*,2*R*)	8(1*R*,2*S*)	67
L_3	50:50	10 (1*S*,2*S*)	9 (1*S*,2*R*)	70
L_4	**63:37**	**83 (1*R*,2*R*)**	**87 (1*R*,2*S*)**	**72**
L_5	65:35	21 (1*R*,2*R*)	20(1*R*,2*S*)	68
L_6	63:37	11 (1*S*,2*S*)	8 (1*R*,2*S*)	63
L_7	66:34	13 (1*R*,2*R*)	11(1*R*,2*S*)	60
L_8	61:39	0	0	65

[a] *Trans*:*cis* ratios were determined by NMR-analysis of the crude reaction mixture.

[b] Determined by HPLC-analysis using a chiral stationary phase.

[c] Determined by optical rotation.

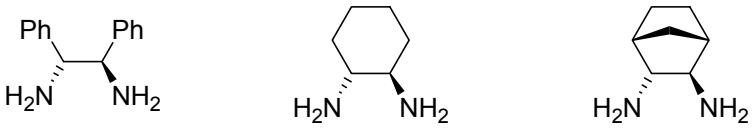
[d] The absolute configuration was confirmed by the sign of the optical rotation.

The *tert*-butyl derivative **L_4** was the most effective ligand, delivering the *trans* and *cis* cyclopropanated products with 83 and 87% ee, respectively. Most probably, in this particular case, the bulky *tert*-butyl groups pointing away from the metal centre are capable of controlling the olefin approach in an efficient manner, while the planar phenyl groups are not. *In situ* generation of the active Cu(I) catalyst by reduction of the Cu(II) complex with phenylhydrazine afforded the products with slightly lower enantioselectivities. Addition of the ethyl diazoacetate at r.t. over 5 h also resulted in a decrease in the enantioselectivity. In contrast, the diastereomeric ligand **L_3** afforded products with 10 and 9% ee, respectively. This is, most probably, due to the steric hindrance induced by two bulky oxazolinyl groups pointing in such a way that does not allow the metal to simultaneously coordinate to both nitrogen atoms of the oxazoline rings. The reaction is probably catalyzed by free or mono-coordinated Cu species, leading to almost racemic products in good yields.

Studies concerning the efficiency of the complex derived from **L_4** in the reaction of different diazoacetate esters with various olefins are currently in progress.

3.4 Chiral 1,2-diamines

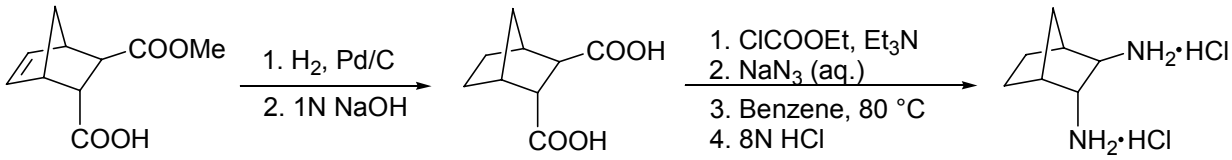
In recent years, the interest in the development of stereocontrolled syntheses of chiral 1,2-diamines has increased considerably.[243] Vicinal diamines have become important synthetic targets, particularly due to their use as intermediates in the preparations of important biologically active compounds such as biotin,[244] balanol,[245] a broad range of κ-opioid receptor agonists,[246] which are used pharmacologically as analgesic agents without the clinical side effects that characterize morphine, and 1,2-diamino platinum complexes, which serve as cytostatic remedies in chemotherapy with increased antitumoral activity and less toxicity as compared to cisplatin.[247] In addition, vicinal diamines have found application in the resolution of racemates,[248] as chiral auxiliaries in the enantio- and diastereoselective syntheses[243] and in the preparation of a large number of ligands for asymmetric catalysis including those for epoxidations,[249] alkene aziridinations,[250] epoxide openings,[251] Diels-Alder reactions[252] and transfer hydrogenations.[239] In the light of their synthetic significance, it is surprising that most of these studies have been focused on the use of a limited number of diamines. The most widely applied ones are *trans*-1,2-diphenylethylene diamine (**252**) and *trans*-1,2-diaminocyclohexane (**253**). They are readily accessible, and their large-scale preparations have been described in full detail.[253] Interestingly, the related *trans*-diamine **254** which has a more rigid norbornane backbone, remained almost unnoticed. Since, in contrast to **252** and **253**, diamine **254** is C_1-symmetric, special effects could result when ligands stemming from **254** are used in asymmetric catalysis. Enantiopure **254** was first isolated only a few years ago, by resolution of its racemate with *O*,*O'*-dibenzoyltartaric acid.[254] Unsatisfyingly, however, this approach afforded the tartaric salt of *ent*-**254** in only 16% yield, based on the racemate. Hence, a more efficient preparation, which would allow a broader application of this interesting 1,2-diamine, was desirable.



252 **253** **254**

Scheme 78: Selected Chiral 1,2-Diamines.

As shown in Scheme 79, our overall reaction sequence involved the asymmetric desymmetrization of *meso*-anhydride **160** followed by selective epimerization of *cis*-hemiester **176** to its *trans*-isomer **255**,[184,231] which is then converted into the saturated diacid **256** by saponification and hydrogenation. Activation of the diacid by treatment with ethyl chloroformate and triethylamine, followed by addition of an aqueous solution of sodium azide afforded the corresponding dicarboxylic diazide which was subjected to thermal rearrangement without further purification. Curtius degradation of the crude diazide in benzene followed by acidic hydrolysis of the resulting isocyanate led to the dihydrochloric salt of diamine **254** in 70% yield.



255, 98% ee **256**, 88% y **254**, 70% y

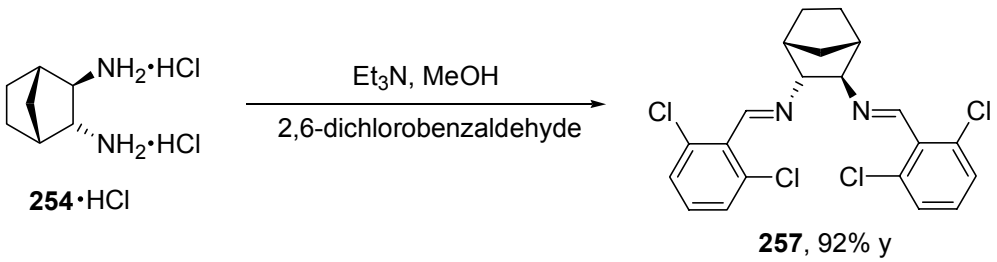
Scheme 79: Synthesis of the Norbornane-Type Diamine Dihydrochloric Salt **254**·2HCl.

The absolute configuration of **254**·2HCl was determined by comparison of its sense of optical rotation with that reported in the literature.[254] Since the value of the optical rotation differed strongly from the published data, the enantiomeric ratio of 99:1 was confirmed by HPLC analysis of the corresponding ditosylate, using a racemic sample of this compound as reference. As a consequence of the stereospecificity of the epimerization and the Curtius degradation, the enantiomeric excess of this product was identical with the one of the starting material **176**.

During the course of our investigations, Trost reported on the application of the diphenylphosphinobenzoyl substituted diamine **254** as a ligand in asymmetric allylic

alkylations.[255] Their synthesis involved a Diels-Alder reaction between (+)-dimenthyl fumarate and cyclopentadiene[256] followed by saponification of the resulting diester and subsequent degradation similar to that shown in Scheme 79.

In contrast to the free diamines,[257] the corresponding dihydrochloric salts are stable to air and easy to handle. Since treatment of **3**·2HCl with KOH and distillation under reduced pressure led to the free diamine in only moderate yield,[254] the preferred method was to liberate **3** *in situ* by addition of an excess of triethylamine before further derivatization. As shown in Scheme 80, direct condensation between 2,4-dichloro-benzaldehyde and the free diamine **254**, led to the salen type ligand **257** in excellent yield.



254·HCl

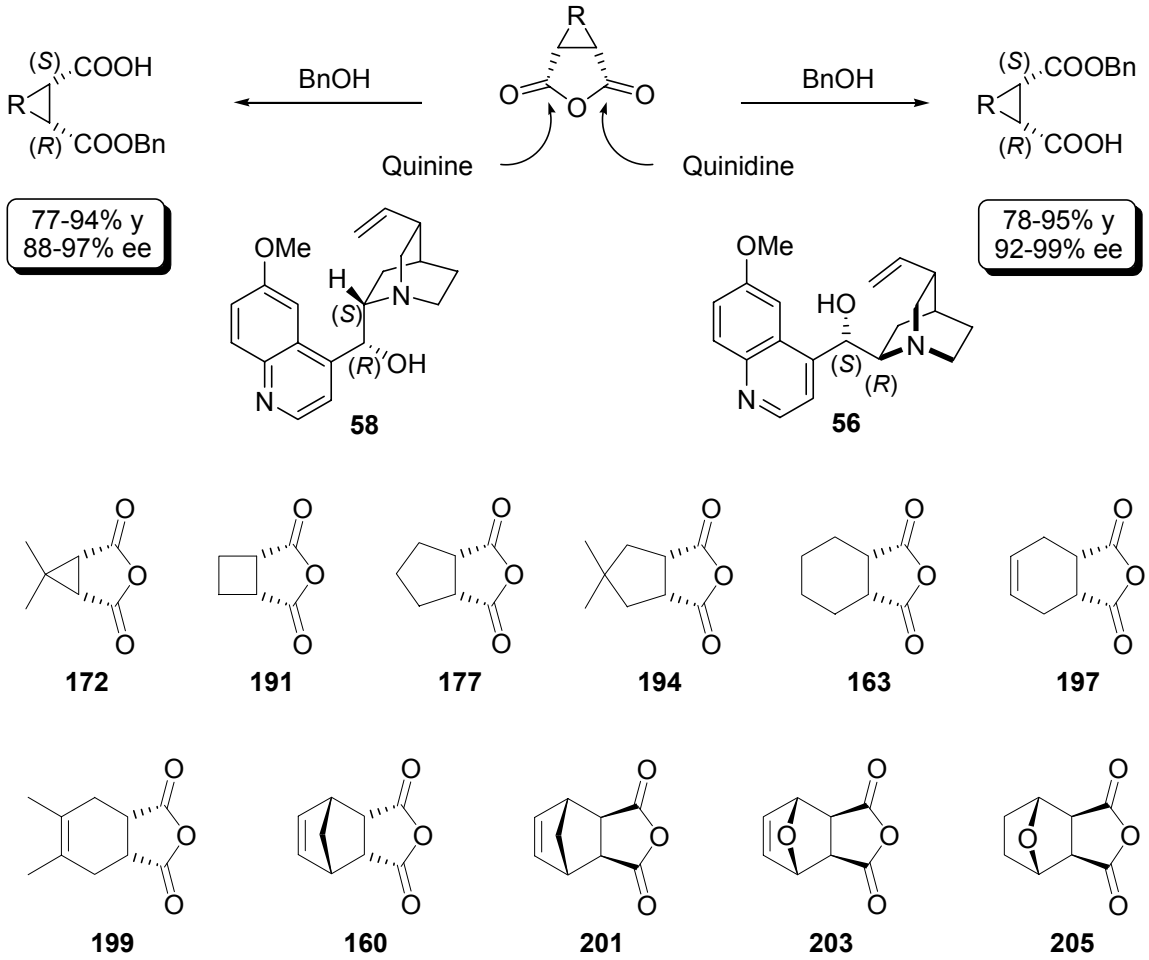
257, 92% y

Scheme 80: Derivatization of the Diamine Dihydrochloric Salt **254**·2HCl.

Currently, we are focusing our efforts on the application of this new compound as ligand in asymmetric catalysis.

4 Summary and outlook

It was demonstrated that the desymmetrization of easily accessible *meso*-anhydrides by cinchona alkaloid-mediated opening with benzyl alcohol[258] is applicable to a variety of structurally different substrates and leads to the corresponding optically active hemiesters with high enantioselectivities (up to 99% ee).[200] A simple reaction protocol was developed which allows the synthesis of either enantiomer selectively, generally without an additional need of purification of the resulting benzyl monoester by chromatography or recrystallization.

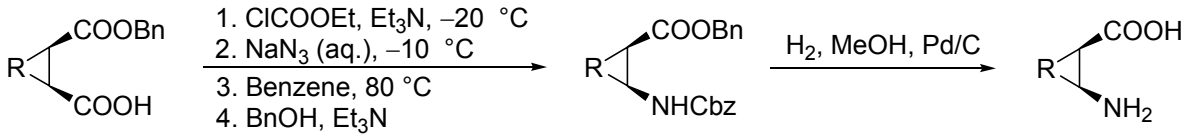


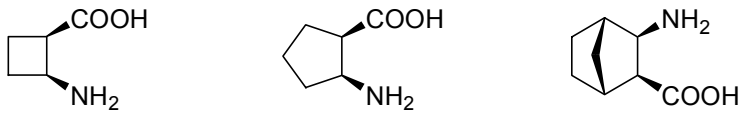
Scheme 81: Stereoselective Desymmetrization: Substrate Spectrum.

The procedure described above is an improved version of previously reported alkaloid mediated asymmetric anhydride openings.[180,181] An advantage of the present

protocol using benzyl alcohol as nucleophile is that it allows the reactions to be performed in toluene as solvent, avoiding the use of the previously applied toxic carbon tetrachloride.

The synthetic usefulness of the method was demonstrated by the preparation of optically active β-amino acids through a reaction sequence involving a Curtius degradation as a key step. Their complete deprotection could be obtained in a single step by simple hydrogenation enabling the isolation of rather sensitive products.[200]



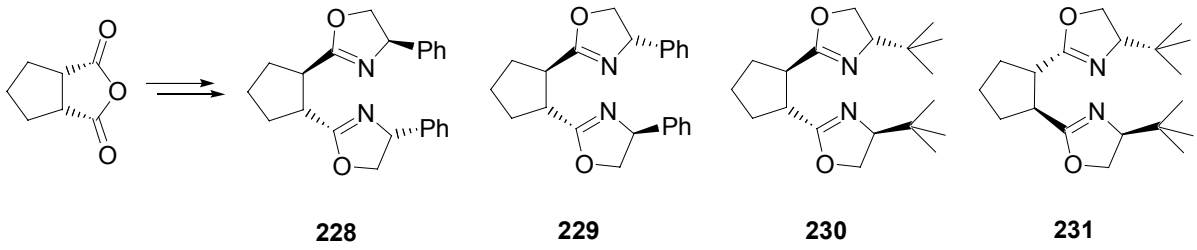


212 **213** **214**

Scheme 82: Synthesis of Enantiomerically Enriched β-Amino Acids.

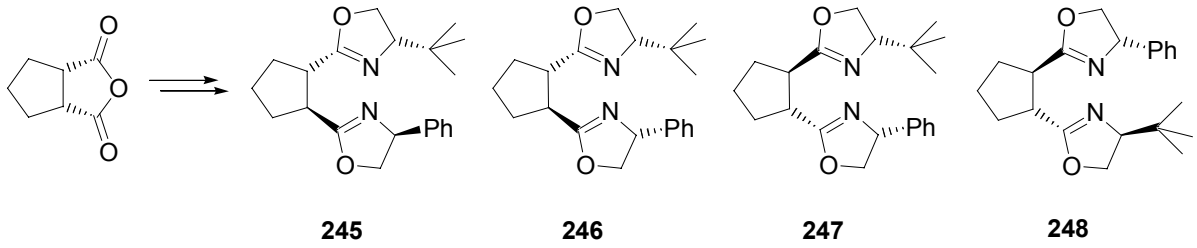
In the initial studies a highly efficient protocol for the cinchona alkaloid mediated enantioselective methanolysis, leading to a broad variety of hemiesters in excellent yields with up to 99% ee has been elaborated. Methylesters of such type have found application in the synthesis of mono- and bicyclic β-amino esters,[181] γ-amino alcohols[182] and 1,2-diamines.[182,183]

As an extension of our work in this field, we have now developed a general strategy for the synthesis of optically active C_2-symmetric bisoxazolines. Accordingly, four cyclopentane derivatives have been prepared in good overall yields (Scheme 83).



Scheme 83: C_2-Symmetric Bisoxazolines.

Furthermore, the presence of an ester and acid functional group in the methylhemiester allows a sequential functionalization. Consequently, C_1-symmetric bisoxazolines are also readily available in good overall yields (Scheme 84).



Scheme 84: C_1-Symmetric Bisoxazolines.

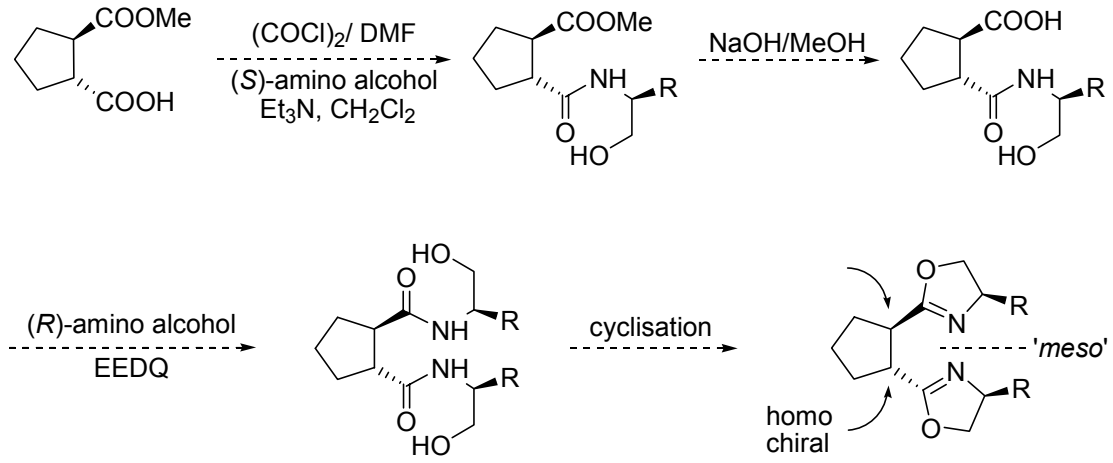
The catalytic activity of the copper (II) and zinc (II) complexes derived from these eight ligands has been tested in the asymmetric Diels-Alder reaction. In addition, the effect of temperature and counterion on the reaction selectivity has been also investigated. Enantioselectivities of up to 75% were attained with the copper complex derived from the C_2-symmetric bisoxazoline **229**. Future studies for optimization of the ligand structure are currently in progress.

The catalytic behavior of the copper (II) complexes has been evaluated also in the related hetero Diels-Alder reaction between 1,3-cyclohexadiene and ethyl glyoxalate. The HDA-adducts were obtained always with high diastereoselectivities (>97% *endo* product) and promising enantioselectivities of 30-49% ee (as determined by GC-analysis).

Enantioselective cyclopropanation of styrene was chosen in order to determine the efficiency of the [Cu(box)]-(OTf) system. In this context it has been demonstrated that the copper (I) complex derived from **231** is capable of controlling the chirality of the CH center which comes from the ethyl diazoacetate, delivering the *trans* and *cis* cyclopropanated products with 83 and 87% ee respectively.

In summary, an efficient method for the asymmetric synthesis of a wide variety of C_2- and C_1-symmetric bisoxazolines was developed.

In future, the same methodology could be also applied in the synthesis of a cyclopentane derivative containing a homo chiral backbone and a *meso*-line configuration of the two oxazoline moieties, which could be of beneficial effect in the above mentioned catalytic reactions (Scheme 85).



Scheme 85: Synthesis of C_1-Symmetric Bisoxazolines with a Chiral Backbone and a *meso*-line Configuration of the two Oxazoline Moieties.

5 Experimental section

5.1 General methods and chemicals

5.1.1 Inert atmosphere conditions

All reactions involving air- or moisture-sensitive compounds were carried out under argon using standard Schlenk and vacuum line techniques.[259] Glassware were heated under vacuum with a heat gun and flushed with argon. Addition of all reagents as well as solvents was carried out with glass or polypropylene syringes equipped with V2A steel needles under argon steam. Labile chemicals were kept in a glove-box or refrigerator and stored under argon.

5.1.2 Solvents

The solvents were dried and distilled under argon according to standard procedures:[260]

Acetone:	was purchased from Fluka and used as received.
Acetonitrile	was purchased from Sigma-Aldrich and used as supplied.
Benzene:	was purchased from Merck and used as received.
Benzyl alcohol:	was purchased from Sigma-Aldrich and used as supplied.
CCl_4:	was purchased from Merck and used as received.
CH_2Cl_2:	was distilled from CaH_2 under Ar.
Diethyl ether:	was predried over KOH distilled from sodium benzophenone ketyl radical under argon.
Methanol:	analytically pure MeOH required for the desymmetrization was purchased from Fluka or Merck and used as supplied.
THF:	was predried over KOH and distilled from sodium benzophenone ketyl radical under argon.

Toluene: was distilled from sodium benzophenone ketyl radical under argon and stored over 4 Å molecular sieves.

Unless otherwise specified, all reagents were purchased from commercial suppliers (Acros, Aldrich, Fisher-Scientific, Fluka, Lancaster, Merck, Strem) and used without further purification. All the amino acids employed in practice, as well as the Pd/C catalyst were received from Degussa.

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), Varian Gemini 300 (300 MHz) or Inova 400 (400 MHz) spectrometer. The chemical shifts are given in ppm using tetramethylsilane (δ = 0.00 ppm) as internal standard, and in the absence of tetramethylsilane, they are based on the deuterated solvent peak (Acetone δ = 2.09 ppm, Chloroform δ = 7.25 ppm, DMSO δ = 2.50 ppm, Methanol δ = 3.34 ppm). The coupling constants *J* are given in Hertz. The following abbreviations are used in order to describe the signals observed in the ^{1}H NMR-spectra: s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), m (multiplet), br (broad signal). The diastereomeric ratio (dr) was determined by analysis of the ^{1}H NMR-spectra of the crude reaction product.

^{13}C NMR-Spectra:

^{13}C NMR-spectra were ^{1}H-broad band-decoupled and measured with a Varian VXR 300 (75 MHz), Varian Gemini 300 (75 MHz) or Inova 400 (100 MHz) spectrometer. The chemical shifts are given in ppm using tetramethylsilane (δ = 0.00 ppm) or the deuterated solvent peak as internal standard.

Mass spectrometry:

Mass spectra were recorded on a Varian MAT 212 and a Finnigan MAT 95 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.

IR-spectroscopy:

Infrared spectra were recorded on a Perkin-Elmer PE-1760 FT apparatus. All bands are given in cm^{-1}. Only the strongest bands (50-100%) are listed.

Optical rotation:

Optical rotations were determined on a Perkin Elmer PE-241 instrument at room temperature (ca. 20 °C) using solvents of Merck UVASOL-quality. The measurements were carried out using a light frequency of 589 nm (D-line of a sodium vapour lamp) in a cuvette (length d = 10 cm; concentration c is given in g/100 mL).

Melting point:

Melting Points were measured in open glass capillaries with a Büchi B-540 apparatus and are uncorrected.

Elemental analysis:

All microanalyses were conducted on a Heraeus CHN RAPID instrument. All values are given as mass percentages.

5.1.4 Chromatography

Thin layer chromatography (TLC):

TLC was performed using precoated aluminium backed sheets (Merck silica gel 60 F_{254}). Detection was performed by using UV radiation (254 nm) or by developing the TLC plate with: (a) a basic solution of $KMnO_4$ in water,

(b) an acidic cerium molybdate solution in ethanol.

Column chromatography:

Separations by column chromatography were conducted according to the suggestion of Still.[261] Silica gel 60 (Merk, mesh 40-63 μm) was employed as stationary phase. All solvents have been distilled prior to use.

Analytic HPLC:

For analyses by means of high performance liquid chromatography a HPLC system from the company Gynkothek was used. The system comprised a GINA 50 Autosampler, a UVD170S UV/VIS detector, a M480G pump and a DG503 degassing apparatus. The peaks were detected *via* the pre-set wavelength. Chiral columns (250 × 4.6 nm) from Daicel Chemical Industries Ltd. were used as stationary phases.

Gas chromatography:

Gas chromatographic analyses with an achiral stationary phase 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. Gas chromatographic analyses for the determination of the enantiomeric excesses were performed on a Hewlett-Packard 5890 Series II with electronic pressure control (EPC). In order to ensure an

unequivocal determination of enantiomeric excesses, the corresponding racemates were separately measured as well. All chromatograms were baseline separated. 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 dependent (EPC; constant flow). Otherwise the pressure given is meant to be a constant pressure on the column.

The enantiomeric excess of the benzyl esters, as well as of the methyl esters, were determined by GC analysis of the corresponding lactones which were obtained by selective reduction of the ester group with $LiBEt_3H$ followed by acid-catalyzed lactonization. Capillary gas chromatograms were obtained using the following column and temperature program: Lipodex E: 2,6-*O*-Dipentyl-3-*O*-butyryl-γ-cyclodextrin (Macherey-Nagel GmbH & Co.KG). Column head pressure: 1.0 bar N_2; 100 °C (50 min), heating rate 3.0 °C/min up to 180 °C (60 min). Injector temperature 200 °C, detector temperature 250 °C.

5.1.5 Compounds synthesized according to literature procedures

Cis-3,3-dimethylcyclopropane-1,2-dicarboxylic anhydride **172**,[262] *cis*-1,2-cyclopentane-dicarboxylic anhydride **177**,[263] *cis*-4,4-dimethylcyclopentane-1,2-dicarboxylic anhydride **194**,[264] *exo*-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride **201**[265] were prepared according to literature procedures.

Cis-1,2-cyclobutanedicarboxylic anhydride was obtained by refluxing *cis*-cyclobutane-1,2-dicarboxylic acid (Fluka) in trifluoroacetic anhydride (Acros Organics) for 16 h. *Endo*-bicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic anhydride **160** and *exo*-7-oxabicyclo [2.2.1]hept-5-ene-2,3-dicarboxylic anhydride **203** were prepared by Diels-Alder reaction of maleic anhydride and the corresponding diene. *Exo*-7-oxabicyclo [2.2.1]hept-5-ane-2,3-dicarboxylic anhydride **205** was prepared by hydrogenation of the unsaturated analogue **203** over 10% Pd/C.

The amino alcohols employed for the bisoxazolines formation were synthesized according to Drauz, Meyers and co-workers.[266]

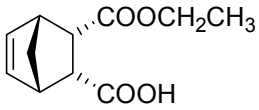
The racemic hemiesters were prepared by opening with the alcohol nucleophile in the presence of 1,4-diazabicyclo[2.2.2]octane (the corresponding alcohol was employed as solvent).

5.2 Asymmetric anhydride opening

5.2.1 General procedure for the alkaloid-mediated ring opening of cyclic *meso*-anhydrides (GP-1)

Benzyl alcohol (0.310 mL, 3.00 mmol) was added dropwise to a stirred suspension of the anhydride (1.00 mmol) and the alkaloid (0.357 g, 1.10 mmol) in a 1:1-mixture of toluene and tetrachloromethane (5.0 mL in the case of quinidine, 20.0 mL in the case of quinine) at –55 °C under argon. The reaction mixture was stirred at this temperature for 60 h. During this period the material gradually dissolved. Subsequently, the resulting clear solution was concentrated in vacuum to dryness and the resulting residue was dissolved in diethyl ether (10.0 mL). The solution was washed with 2 N HCl (3 × 3.0 mL), followed by extraction of the aqueous phase with diethyl ether (5 × 5.0 mL) and the combined organic layers were extracted with a saturated solution of sodium carbonate (5 × 15.0 mL). The resulting aqueous phase was washed with diethyl ether (1 × 25.0 mL) in order to remove traces of benzyl alcohol, acidified with conc. HCl, extracted with CH_2Cl_2 (5 × 20.0 mL) and the organic phase was dried over $MgSO_4$, filtered and concentrated providing the corresponding hemiester. Analogously, the quinidine- and quinine-mediated opening was performed in pure toluene using 5.0 or 10.0 mL solvent/mmol anhydride, respectively. To recover the alkaloid, the acidic aqueous phase was neutralized with Na_2CO_3 and extracted with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$ and filtered. Evaporation of the solvent yielded the alkaloid almost quantitatively.

5.2.2 Synthesis of (2*R*,3*S*)-3-*endo*-ethoxycarbonyl-bicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylic acid (184)



The product was obtained according to GP-1 from the quinidine opening of anhydride **160** in the presence of ethanol in 97% yield (204 mg, 0.970 mmol).

Mp: 71 °C (rac), colorless oil (en), lit.[267] mp: 74-75 °C (rac).

$[\alpha]^{rt}_D$ = –5.8 (*c* = 3.13, $CHCl_3$).

ee = 89% [GC-analysis of the lactone: Lipodex E, t_1 = 80.7, t_2 = 81.1 (major)].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.20 (br t, *J* = 7.2 Hz, 3H), 1.34 (br d, *J* = 8.6 Hz, 1H), 1.48 (dt, *J* = 1.7, 8.6 Hz, 1H), 3.17-3.18 (m, 2H), 3.27 (dd, *J* = 2.7, 10.1 Hz, 1H), 3.33 (dd, *J* = 3.0, 10.1 Hz, 1H), 4.03 (dq, *J* = 7.1, 10.8 Hz, 1H), 4.07 (dq, *J* = 7.1, 10.8 Hz, 1H), 6.21 (dd, *J* = 3.0, 5.7 Hz, 1H), 6.31 (dd, *J* = 3.0, 5.7 Hz, 1H), 10.54 (br s, 1H).

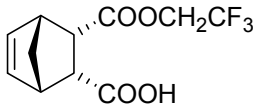
^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.3, 46.4, 46.8, 48.3, 48.7, 49.0, 60.6, 134.6, 135.7, 172.6, 179.0.

IR (KBr): 2980, 1736, 1701, 1259, 1215, 1181 cm^{-1}.

EI-MS: m/z = 210 (M^+, 1), 192 (5), 165 (24), 164 (11), 145 (36), 137 (13), 127 (9), 119 (21), 99 (22), 91 (22), 66 (100), 65 (11).

Elemental Analysis for $C_{11}H_{14}O_4$ (210.23): Calcd.: C 62.85; H 6.71.
Found: C 62.83; H 6.71.

5.2.3 Synthesis of 3-*endo*-(2',2',2'-trifluorethoxycarbonyl)-bicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylic acid (185)



The product was obtained according to GP-1 from the quinidine opening of anhydride **160** in the presence of 2,2,2-trifluoroethanol in 96% yield (254 mg, 0.961 mmol) in a racemic form.

Mp: 87.5 °C (rac).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.37 (d, *J* = 8.6 Hz, 1H), 1.54 (dt, *J* = 1.7, 8.6 Hz, 1H), 3.22 (br d, *J* = 10.1 Hz, 2H), 3.25 (dd, *J* = 3.0, 10.1 Hz, 1H), 3.41 (dd, *J* = 3.2, 10.1 Hz, 1H), 4.23 (dq, *J* = 8.6, 12.6 Hz, 1H), 4.47 (dq, *J* = 8.6, 12.6 Hz, 1H), 6.21 (dd, *J* = 3.0, 5.4 Hz, 1H), 6.34 (dd, *J* = 3.0, 5.4 Hz, 1H), 10.39 (br s, 1H).

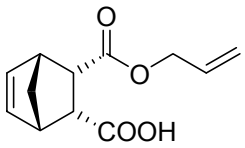
^{13}C NMR (75 MHz, $CDCl_3$): δ = 46.1, 46.7, 47.7, 48.2, 48.8, 60.4 (q, *J* = 36.5 Hz), 121.2 (q, *J* = 277.0 Hz), 134.5, 135.6, 171.0, 178.5.

IR (KBr): 2981, 1757, 1707, 1417, 1312, 1277, 1260, 1230, 1212, 1168, 1088 cm^{-1}.

EI-MS: m/z = 164 (12), 120 (12), 119 (9), 92 (36), 91 (100).

Elemental Analysis for $C_{11}H_{11}F_3O_4$ (264.20): Calcd.: C 50.01; H 4.20.
Found: C 50.28; H 4.30.

5.2.4 Synthesis of (2*R*,3*S*)-3-*endo*-allyloxycarbonyl-bicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylic acid (186)



The product was obtained according to GP-1 from the quinidine opening of anhydride **160** in the presence of allyl alcohol in 97% yield (223 mg, 0.973 mmol).

Mp: 84 °C (rac), colorless oil (en), lit.[268] mp: 83 °C (rac).

$[\alpha]^{rt}_D$ = −1.7 (*c* = 3.20, $CHCl_3$).

ee = 97% [GC-analysis of the lactone: Lipodex E, t_1 = 80.7, t_2 = 81.1 (major)].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.34 (d, *J* = 8.6 Hz, 1H), 1.49 (dt, *J* = 1.7, 8.6 Hz, 1H), 3.18 (br s, 2H), 3.28-3.36 (m, 2H), 4.45 (ddt, *J* = 1.5, 5.9, 13.1 Hz, 1H), 4.54 (ddt, *J* = 1.5, 5.9, 13.1 Hz, 1H), 5.17-5.22 (m, 1H), 5.25-5.32 (m, 1H), 5.87 (ddt, *J* = 5.9, 10.4, 16.3 Hz, 1H), 6.21 (dd, *J* = 3.0, 5.5 Hz, 1H), 6.31 (dd, *J* = 3.0, 5.5 Hz, 1H), 10.67 (br s, 1H).

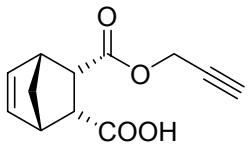
^{13}C NMR (75 MHz, $CDCl_3$): δ = 46.4, 46.8, 48.3, 48.6, 49.0, 65.5, 118.5, 132.4, 134.6, 135.7, 172.3, 178.9.

IR (KBr): 2980, 1736, 1703, 1342, 1261, 1216, 1173, 1153, 930 cm^{-1}.

EI-MS: m/z = 222 (M^+, 2), 204 (3), 176 (6), 165 (7), 157 (31), 139 (16), 137 (13), 119 (14), 99 (18), 91 (19), 66 (100), 65 (4).

Elemental Analysis for $C_{12}H_{14}O_4$ (229.24): Calcd.: C 64.85; H 6.35.
Found: C 64.79; H 6.35.

5.2.5 Synthesis of (2*R*,3*S*)-3-*endo*-propargyloxycarbonyl-bicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylic acid (187)



The product was obtained according to GP-1 from the quinidine opening of anhydride **160** in the presence of propargyl alcohol in 97% yield (214 mg, 0.972 mmol).

Mp: 115 °C (rac), colorless oil (en).

$[\alpha]^{rt}_D$ = −1.40 (*c* = 3.06, $CHCl_3$).

ee = 79% [GC-analysis of the lactone: Lipodex E, t_1 = 80.7, t_2 = 81.1 (major)].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.34 (d, *J* = 8.6 Hz, 1H), 1.50 (dt, *J* = 1.7, 8.6 Hz, 1H), 2.47 (t, *J* = 2.5 Hz, 1H), 3.19-3.21 (m, 2H), 3.30 (dd, *J* = 3.0, 10.1 Hz, 1H), 3.37 (dd, *J* = 3.2, 10.1 Hz, 1H), 4.53 (dd, *J* = 2.5, 15.8 Hz, 1H), 4.67 (dd, *J* = 2.5, 15.8 Hz, 1H), 6.21 (dd, *J* = 3.0, 5.7 Hz, 1H), 6.34 (dd, *J* = 3.0, 5.7 Hz, 1H), 10.70 (br s, 1H).

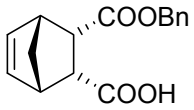
^{13}C NMR (75 MHz, $CDCl_3$): δ = 46.3, 46.9, 48.1, 48.4, 49.0, 52.1, 75.1, 77.9, 134.6, 135.8, 171.8, 178.5.

IR (KBr): 3284, 1744, 1705, 1344, 1260, 1216, 1169, 1073 cm^{-1}.

EI-MS: m/z = 220 (M^+, 1), 175 (3), 165 (5), 155 (22), 137 (13), 119 (12), 99 (20), 91 (16), 66 (100).

Elemental Analysis for $C_{12}H_{12}O_4$ (220.22): Calcd.: C 65.45; H 5.49.
Found: C 65.24; H 5.60.

5.2.6 Synthesis of (2*R*,3*S*)-3-*endo*-benzyloxycarbonyl-bicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylic acid (188)



The product was obtained according to GP-1 from the quinidine opening of anhydride **160** in 92% yield (250 mg, 0.918 mmol) as a white solid.

Mp: 120 °C (rac), 92 °C (en).

$[\alpha]^{rt}_D$ = +8.0 (*c* = 1.95, $CHCl_3$).

ee = 97% [GC-analysis of the lactone: Lipodex E, t_1 = 80.7, t_2 = 81.1 (major)].

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.32 (d, *J* = 8.5 Hz, 1H), 1.47 (dt, *J* = 1.7, 8.5 Hz, 1H), 3.18 (br s, 2H), 3.30-3.32 (m, 2H), 4.92/5.09 (AB-system, *J* = 12.4 Hz, 2H), 6.21 (dd, *J* = 3.0, 5.7 Hz, 1H), 6.28 (dd, *J* = 3.0, 5.7 Hz, 1H), 7.27-7.36 (m, 5H), 9.50 (br s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 46.4, 46.8, 48.4, 48.6, 49.0, 66.7, 128.4, 128.6, 128.7, 134.7, 135.7, 136.2, 172.5, 178.8.

IR (KBr): 3034, 2989, 2944, 1747, 1701, 1436, 1340, 1262, 1226, 1173, 1143, 1028 cm^{-1}.

EI-MS: m/z = 272 (M^+, 2), 254 (3), 226 (3), 181 (58), 163 (3), 137 (5), 119 (2), 91 (100), 66 (20).

Elemental Analysis for $C_{16}H_{16}O_4$ (272.30): Calcd.: C 70.57; H 5.92.
Found: C 70.55; H 6.01.

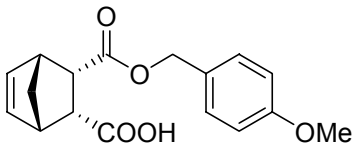
5.2.7 Synthesis of (2*S*,3*R*)-3-*endo*-benzyloxycarbonyl-bicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylic acid (*ent*-188)

The product was obtained according to GP-1 from the quinine opening of anhydride **160** in 93% yield (253 mg, 0.929 mmol) as a white solid.

[α]$^{rt}_{D}$ = –7.4 (*c* = 1.00, $CHCl_3$).

ee = 96% [GC-analysis of the lactone: Lipodex E, t_1 = 80.7 (major), t_2 = 81.1].

5.2.8 Synthesis of (2*R*,3*S*)-3-*endo*-(4-methoxy-benzyloxycarbonyl)-bicyclo [2.2.1]hept-5-ene-2-*endo*-carboxylic acid (189)



The product was obtained according to GP-1 from the quinidine opening of anhydride **160** in the presence of *p*-anisyl alcohol in 93% yield (282 mg, 0.933 mmol).

Mp: 94 °C (rac), colorless oil (en).

[α]$^{rt}_{D}$ = +7.3 (*c* = 3.06, $CHCl_3$).

ee = 97% [GC-analysis of the lactone: Lipodex E, t_1 = 80.7, t_2 = 81.1 (major)].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.32 (br d, *J* = 8.6 Hz, 1H), 1.48 (dt, *J* = 1.7, 8.6 Hz, 1H), 3.18 (br d, *J* = 8.9 Hz, 2H), 3.31-3.32 (m, 2H), 3.79 (s, 3H), 4.87/5.03 (AB-system, *J* = 12.1 Hz, 2H), 6.22 (dd, *J* = 3.0, 5.4 Hz, 1H), 6.28 (dd, *J* = 3.0, 5.4 Hz, 1H), 6.84-6.89 (m, 2H), 7.22-7.27 (m, 2H), 10.25 (br s, 1H).

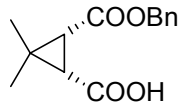
^{13}C NMR (75 MHz, $CDCl_3$): δ = 46.4, 46.8, 48.4, 48.6, 49.0, 55.5, 66.5, 114.1, 128.3, 130.4, 134.6, 135.8, 159.8, 172.5, 178.8.

IR (KBr): 2952, 1733, 1706, 1516, 1265, 1215, 1165, 1073 cm^{-1}.

EI-MS: m/z = 302 (M^+, 8), 121 (100), 91 (6).

Elemental Analysis for $C_{17}H_{18}O_5$ (302.32): Calcd.: C 67.54; H 6.00.
Found: C 67.49; H 6.08.

5.2.9 Synthesis of (1*S*,2*R*)-*cis*-2-benzyloxycarbonyl-3,3-dimethylcyclopropane-1-carboxylic acid (190)



The product was obtained according to GP-1 from the quinidine opening of anhydride **172** in 95% yield (259 mg, 0.951 mmol).

Mp: 79 °C (rac), colorless oil (en).

$[\alpha]^{rt}_D$ = −1.8 (*c* = 1.58, $CHCl_3$).

ee = 92% [GC-analysis of the lactone: Lipodex E, column head pressure: 0.6 bar N_2, 100 °C (20 min), heating rate 1.0 °C/min up to 140 °C (20 min), heating rate 20.0 °C/min up to 180 °C (3 min), t_1 = 61.1, t_2 = 64.6 (major)].

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26 (s, 3H), 1.41 (s, 3H), 1.96/1.99 (AB-system, *J* = 8.8 Hz, 2H), 5.12/5.17 (AB-system, *J* = 12.1 Hz, 2H), 7.30-7.38 (m, 5H), 10.60 (br s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.6, 27.7, 28.4, 33.1, 33.1, 67.4, 128.6, 128.7, 128.8, 135.6, 170.7, 174.1.

IR (KBr): 3042, 2961, 2881, 1741, 1691, 1502, 1445, 1257, 1191, 1097 cm^{-1}.

EI-MS: m/z = 248 (M^+, 7), 230 (1), 202 (1), 142 (5), 141 (3), 113 (19), 108 (7), 95 (4), 91 (100), 67 (3), 65 (6).

Elemental Analysis for $C_{14}H_{16}O_4$ (272.30): Calcd.: C 67.73; H 6.50.
Found: C 67.67; H 6.54.

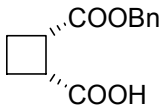
5.2.10 Synthesis of (1*R*,2*S*)-*cis*-2-benzyloxycarbonyl-3,3-dimethylcyclopropane-1-carboxylic acid (*ent*-190)

The product was obtained from the quinine opening of anhydride **172** in 94% yield (257 mg, 0.944 mmol) as a colorless oil.

$[\alpha]^{rt}_D$ = +1.7 (*c* = 1.00, $CHCl_3$).

ee = 88% [GC-analysis of the lactone: Lipodex E, column head pressure: 0.6 bar N_2, 100 °C (20 min), heating rate 1.0 °C/min up to 140 °C (20 min), heating rate 20.0 °C/min up to 180 °C (3 min), t_1 = 61.1 (major), t_2 = 64.6].

5.2.11 Synthesis of (1*R*,2*S*)-*cis*-2-benzyloxycarbonyl-cyclobutane-1-carboxylic acid (192)



The product was obtained according to GP-1 from the quinidine opening of anhydride **191** in 90% yield (210 mg, 0.896 mmol).

Mp: 72.5 °C (rac), colorless oil (en), lit.[269] mp: 66 °C (rac).

$[\alpha]^{rt}_D$ = −10.9 (*c* = 1.75, MeOH).

ee = 93% [GC-analysis of the lactone: Lipodex E, t_1 = 64.4 (major), t_2 = 64.9].

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.17-2.28 (m, 2H), 2.36-2.45 (m, 2H), 3.41-3.49 (m, 2H), 5.08/5.13 (AB-system, *J* = 12.1 Hz, 2H), 7.26-7.36 (m, 5H), 10.10 (br s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.4, 22.5, 40.8, 40.9, 66.9, 128.4, 128.5, 128.7, 135.9, 173.1, 179.3.

IR (KBr): 2955, 1744, 1700, 1336, 1307, 1242, 1189, 1055 cm^{-1}.

EI-MS: m/z = 234 (M^+, 7), 216 (4), 188 (1), 127 (30), 110 (47), 108 (91), 99 (16), 91 (100), 82 (13), 77 (9), 66 (19), 55 (34).

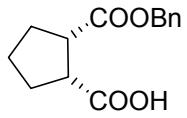
Elemental Analysis for $C_{13}H_{14}O_4$ (234.25): Calcd.: C 66.66; H 6.02.
Found: C 66.72; H 6.02.

5.2.12 Synthesis of (1*S*,2*R*)-*cis*-2-benzyloxycarbonyl-cyclobutane-1-carboxylic acid (*ent*-192)

The product was obtained from the quinine opening of anhydride **191** in 85% yield (200 mg, 0.854 mmol) as a colorless oil.

$[\alpha]^{rt}_D$ = +11.5 (*c* = 1.25, MeOH).
ee = 90% [GC-analysis of the lactone: Lipodex E, t_1 = 64.4, t_2 = 64.9 (major)].

5.2.13 Synthesis of (1*R*,2*S*)-*cis*-2-benzyloxycarbonyl-cyclopentane-1-carboxylic acid (193)



The product was obtained according to GP-1 from the quinidine opening of anhydride **177** in 93% yield (231 mg, 0.930 mmol).

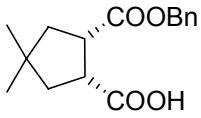
Mp: 37.5 °C (rac), colorless oil (en).
$[\alpha]^{rt}_D$ = +0.6 (*c* = 1.65, $CHCl_3$), $[\alpha]^{rt}_D$ = +1.8 (*c* = 0.94, MeOH).
ee = 97% [GC-analysis of the lactone: Lipodex E, t_1 = 68.6 (major), t_2 = 69.6].
^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.56-1.71 (m, 1H), 1.79-2.11 (m, 5H), 3.03-3.14 (m, 2H), 5.05/5.11 (AB-system, *J* = 12.4 Hz, 2H), 7.25-7.37 (m, 5H), 11.30 (br s, 1H).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.0, 29.0, 47.1, 66.1, 66.7, 128.4, 128.4, 128.7, 136.1, 173.9, 180.7.
IR (capillary): 2961, 1736, 1706, 1183 cm^{-1}.
EI-MS: m/z = 248 (M^+, 8), 230 (6), 202 (9), 141 (46), 108 (100), 107 (89), 95 (19), 91 (87), 67 (27), 65 (16).
Elemental Analysis for $C_{14}H_{16}O_4$ (248.27): Calcd.: C 67.73; H 6.50.
Found: C 67.62; H 6.58.

5.2.14 Synthesis of (1*S*,2*R*)-*cis*-2-benzyloxycarbonyl-cyclopentane-1-carboxylic acid (*ent*-193)

The product was obtained from the quinine opening of anhydride **177** in 89% yield (220 mg, 0.886 mmol) as a colorless oil.

$[\alpha]^{rt}_D$ = −1.3 (*c* = 0.90, MeOH).
ee = 95% [GC-analysis of the lactone: Lipodex E, t_1 = 68.6, t_2 = 69.6 (major)].

5.2.15 Synthesis of (1*R*,2*S*)-*cis*-2-benzyloxycarbonyl-4,4-dimethylcyclo-pentane-1-carboxylic acid (195)



The product was obtained from the quinidine opening of anhydride **194** according to GP-1 with a modified work-up: the crude product, obtained after washing the organic layer with 2 N HCl and evaporation of the solvent, was purified by column chromatography (pentane:EtOAc, 6:1 to 2:1) to give the hemiester **195** in 78% yield (215 mg, 0.778 mmol).

Mp: 61 °C (rac), colorless oil (en).
$[\alpha]^{rt}_D$ = +4.2 (*c* = 1.00, MeOH).
ee = 97% [GC-analysis of the lactone: Lipodex E, t_1 = 68.2, t_2 = 70.0 (major)].
^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.90 (s, 3H), 1.03 (s, 3H), 1.69-1.76 (dd, *J* = 8.2, 13.4 Hz, 2H), 1.82-1.89 (dd, *J* = 8.4, 11.4 Hz, 2H), 3.11-3.24 (m, 2H), 4.95/5.05 (AB-system, *J* = 12.4 Hz, 2H), 7.20-7.30 (m, 5H), 9.40 (br s, 1H).
^{13}C NMR (75 MHz, $CDCl_3$): δ = 29.0, 29.7, 38.8, 43.7, 46.3, 66.8, 128.4, 128.5, 128.7, 136.1, 174.2, 180.8.
IR (KBr): 2958, 2930, 1736, 1702, 1285, 1207 cm^{-1}.

EI-MS: m/z = 276 (M^+, 4), 258 (5), 230 (6), 169 (45), 123 (10), 108 (100), 107 (16), 95 (31), 91 (67), 65 (10).

Elemental Analysis for $C_{16}H_{20}O_4$ (276.33): Calcd.: C 69.54; H 7.30.
Found: C 69.53; H 7.19.

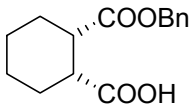
5.2.16 Synthesis of (1*S*,2*R*)-*cis*-2-benzyloxycarbonyl-4,4-dimethylcyclopentane-1-carboxylic acid (*ent*-195)

The product was obtained analogously to **5.2.15** from the quinine opening of anhydride **194** in 83% yield (230 mg, 0.832 mmol) as a colorless oil.

$[\alpha]^{rt}_D$ = –3.9 (*c* = 1.00, MeOH).

ee = 95% [GC-analysis of the lactone: Lipodex E, t_1 = 68.2 (major), t_2 = 70.0].

5.2.17 Synthesis of (1*R*,2*S*)-*cis*-2-benzyloxycarbonyl-cyclohexane-1-carboxylic acid (196)



The product was obtained according to GP-1 from the quinidine opening of anhydride **163** in 88% yield (230 mg, 0.877 mmol) as a colorless oil.

$[\alpha]^{rt}_D$ = +2.9 (*c* = 1.95, $CHCl_3$).

ee = 95% [GC-analysis of the lactone: Lipodex E, t_1 = 71.7 (major), t_2 = 73.1].

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.36-1.56 (m, 4H), 1.76-1.80 (m, 2H), 2.01-2.07 (m, 2H), 2.86-2.89 (m, 2H), 5.09/5.15 (AB-system, *J* = 12.4 Hz, 2H), 7.26-7.35 (m, 5H), 10.70 (br s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 23.9, 24.0, 26.3, 26.5, 42.7, 42.8, 66.6, 128.3, 128.3, 128.7, 136.2, 173.6, 180.5.

IR (capillary): 3064, 3034, 2940, 2864, 1733, 1740, 1453, 1256, 1218, 1176 cm^{-1}.

EI-MS: m/z = 262 (M^+, 8), 244 (8), 216 (3), 155 (30), 108 (89), 107 (87), 91 (99), 81 (40), 45 (100).

Elemental Analysis for $C_{15}H_{18}O_4$ (262.30): Calcd.: C 68.68; H 6.92.
Found: C 68.70; H 6.98.

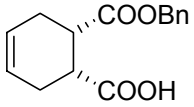
5.2.18 Synthesis of (1*S*,2*R*)-*cis*-2-benzyloxycarbonyl-cyclohexane-1-carboxylic acid (*ent*-196)

The product was obtained from the quinine opening of anhydride **163** in 84% yield (221 mg, 0.843 mmol) as a colorless oil.

$[\alpha]^{rt}_D$ = –2.8 (*c* = 1.09, $CHCl_3$).

ee = 93% [GC-analysis of the lactone: Lipodex E, t_1 = 71.7, t_2 = 73.1 (major)].

5.2.19 Synthesis of (1*R*,2*S*)-*cis*-2-benzyloxycarbonyl-cyclohex-4-ene-1-carboxylic acid (198)



The product was obtained according to GP-1 from the quinidine opening of anhydride **197** in 84% yield (219 mg, 0.841 mmol).

Mp: 65-67 °C (rac), colorless oil (en).

$[\alpha]^{rt}_D$ = +11.0 (*c* = 1.13, MeOH).

ee = 94% [GC-analysis of the lactone: Lipodex E, t_1 = 75.1 (major), t_2 = 75.7].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.32-2.43 (m, 2H), 2.52-2.68 (m, 2H), 3.08-3.13 (m, 2H), 5.12/5.15 (AB-system, *J* = 12.4 Hz, 2H), 5.64-5.72 (m, 2H), 7.26-7.37 (m, 5H), 10.10 (br s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.8, 26.0, 39.8, 39.9, 66.8, 125.3, 125.4, 128.3, 128.4, 128.7, 136.1, 173.3, 180.0.

IR (capillary): 3031, 2924, 1735, 1707, 1296, 1255, 1190, 1163 cm^{-1}.

EI-MS: m/z = 260 (M^+, 1), 242 (13), 214 (11), 169 (4), 123 (18), 107 (5), 91 (100), 79 (26), 65 (9).

Elemental Analysis for $C_{15}H_{16}O_4$ (260.29): Calcd.: C 69.22; H 6.20.
Found: C 68.83; H 6.27.

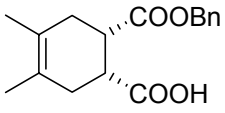
5.2.20 Synthesis of (1*S*,2*R*)-*cis*-2-benzyloxycarbonyl-cyclohex-4-ene-1-carboxylic acid (*ent*-198)

The product was obtained from the quinine opening of anhydride **197** in 84% yield (218 mg, 0.838 mmol) as a colorless oil.

$[\alpha]^{rt}_D$ = −12.1 (*c* = 1.00, MeOH).

ee = 95% [GC-analysis of the lactone: Lipodex E, t_1 = 75.1, t_2 = 75.7 (major)].

5.2.21 Synthesis of (1*R*,2*S*)-*cis*-2-benzyloxycarbonyl-4,5-dimethylcyclohex-4-ene-1-carboxylic acid (200)



The product was obtained according to GP-1 from the quinidine opening of anhydride **199** in 88% yield (255 mg, 0.884 mmol).

Mp: 81-83 °C (rac), colorless oil (en).

$[\alpha]^{rt}_D$ = +1.9 (*c* = 4.87, $CHCl_3$).

ee = 98% [GC-analysis of the lactone: Lipodex E, t_1 = 76.6 (major), t_2 = 77.4].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.60 (s, 6H), 2.27-2.30 (m, 2H), 2.44-2.55 (m, 2H), 3.03-3.07 (m, 2H), 5.09/5.16 (AB-system, *J* = 12.4 Hz, 2H), 7.25-7.37 (m, 5H), 9.80 (br s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 19.1, 19.2, 31.9, 32.1, 40.5, 40.6, 66.7, 124.2, 124.3, 128.2, 128.3, 128.7, 136.2, 173.4, 180.1.

IR (capillary): 2916, 2859, 1736, 1706, 1255, 1197, 1173 cm^{-1}.

EI-MS: m/z = 288 (M^+, 12), 270 (3), 242 (5), 197 (33), 179 (15), 151 (86), 107 (100), 91 (92), 79 (8), 65 (15).

Elemental Analysis for $C_{17}H_{20}O_4$ (288.34): Calcd.: C 70.81; H 6.99.
Found: C 70.70; H 6.64.

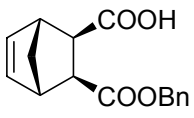
5.2.22 Synthesis of (1*S*,2*R*)-*cis*-2-benzyloxycarbonyl-4,5-dimethylcyclohex-4-ene-1-carboxylic acid (*ent*-200)

The product was obtained from the quinine opening of anhydride **199** in 87% yield (250 mg, 0.867 mmol) as a colorless oil.

$[\alpha]^{rt}_D$ = –2.3 (*c* = 1.00, $CHCl_3$).

ee = 97% [GC-analysis of the lactone: Lipodex E, t_1 = 76.6, t_2 = 77.4 (major)].

5.2.23 Synthesis of (2*R*,3*S*)-3-*exo*-benzyloxycarbonyl-bicyclo[2.2.1]hept-5-ene-2-*exo*-carboxylic acid (202)



The product was obtained according to GP-1 from the quinidine opening of anhydride **201** in 95% yield (258 mg, 0.947 mmol).

Mp: 115 °C (rac), 77 °C (en).

$[\alpha]^{rt}_D$ = –24.6 (*c* = 1.17, $CHCl_3$).

ee = 96% [GC-analysis of the lactone: Lipodex E, t_1 = 73.8, t_2 = 74.8 (major)].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.50 (dt, *J* = 1.7, 9.1 Hz, 1H), 2.13 (d, *J* = 9.1 Hz, 1H), 2.64 (dd, *J* = 1.7, 9.6 Hz, 1H), 2.69 (dd, *J* = 1.7, 9.6 Hz, 1H), 3.10-3.13 (m, 2H), 5.00/5.13 (AB-system, *J* = 12.4 Hz, 2H), 6.21 (br t, *J* = 1.7 Hz, 2H), 7.26-7.37 (m, 5H), 10.40 (br s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 45.6, 45.8, 46.1, 47.7, 47.8, 67.0, 128.4, 128.5, 128.8, 136.0, 138.2, 138.3, 173.5, 180.2.

IR (KBr): 2979, 1744, 1694, 1437, 1327, 1259, 1223, 1186, 1151, 1018 cm^{-1}.

EI-MS: m/z = 272 (M^+, 3), 254 (7), 226 (1), 181 (5), 165 (9), 163 (7), 120 (9), 108 (47), 91 (100), 66 (40).

Elemental Analysis for $C_{16}H_{16}O_4$ (272.30): Calcd.: C 70.57; H 5.92.
Found: C 70.67; H 5.99.

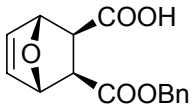
5.2.24 Synthesis of (2*S*,3*R*)-3-*exo*-benzyloxycarbonyl-bicyclo[2.2.1]hept-5-ene-2-*exo*-carboxylic acid (*ent*-202)

The product was obtained from the quinine opening of anhydride **201** in 81% yield (221 mg, 0.812 mmol) as a white solid.

$[\alpha]^{rt}_D$ = +21.6 (*c* = 1.00, $CHCl_3$).

ee = 92% [GC-analysis of the lactone: Lipodex E, t_1 = 73.8 (major), t_2 = 74.8].

5.2.25 Synthesis of (2*S*,3*R*)-3-*exo*-benzyloxycarbonyl-7-oxabicyclo[2.2.1]hept-5-ene-2-*exo*-carboxylic acid (204)



It was obtained from the quinidine opening of anhydride **203** according to GP-1 with a modified work-up: the crude product, obtained after washing the organic layer with 2 N HCl and evaporation of the solvent, was purified by column chromatography (pentane:EtOAc, 2:1 followed by CH_2Cl_2:Et_2O, 1:1 +1% AcOH) to give the hemiester **204** in 84% yield (230 mg, 0.839 mmol) as a white solid. In order to determine the ee, the benzylmonoester was converted by DCC-coupling into the corresponding methyl-benzyldiester which has been hydrogenated over Pd/C to yield the saturated methylmonoester. Next, the corresponding lactone has been analyzed by GC.

Mp: 121 °C (rac), 123 °C (en).

$[\alpha]^{rt}_D$ = –27.8 (*c* = 3.23, MeOH).

ee = 99%. [GC-analysis of the lactone: Lipodex E, t_1 = 95.9 (major), t_2 = 98.7].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.84/2.89 (AB-system, *J* = 8.9 Hz, 2H), 5.06/5.17 (AB-system, *J* = 12.4 Hz, 2H), 5.25 (br s, 1H), 5.32 (br s, 1H), 6.43-6.48 (m, 2H), 7.28-7.38 (m, 5H), 8.50 (br s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 46.9, 47.3, 67.2, 80.4, 80.7, 128.4, 128.5, 128.6, 135.5, 136.4, 136.8, 171.1, 176.8.

IR (KBr): 3022, 1737, 1677, 1334, 1313, 1288, 1214, 1198, 1168, 1008 cm^{-1}.

EI-MS: m/z = 228 (1), 206 (19), 139 (9), 121 (6), 108 (23), 107 (81), 100 (55), 91 (100), 79 (30), 68 (90), 65 (26), 55 (12), 51 (14).

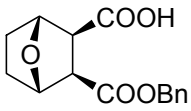
Elemental Analysis for $C_{15}H_{14}O_5$ (274.24): Calcd.: C 65.69; H 5.15.
Found: C 65.69; H 5.33.

5.2.26 Synthesis of (2*R*,3*S*)-3-*exo*-benzyloxycarbonyl-7-oxabicyclo[2.2.1]hept-5-ene-2-*exo*-carboxylic acid (*ent*-204)

The product was obtained analogously to **5.2.25** from the quinine opening of anhydride **203** in 77% yield (211 mg, 0.769 mmol) as a white solid.

$[\alpha]^{rt}_D$ = +29.8 (*c* = 1.00, MeOH).
ee = 94% [GC-analysis of the lactone: Lipodex E, t_1 = 95.9 t_2 = 98.7 (major)].

5.2.27 Synthesis of (2*S*,3*R*)-3-*exo*-benzyloxycarbonyl-7-oxabicyclo[2.2.1] heptane-2-*exo*-carboxylic acid (206)



It was obtained from the quinidine opening of anhydride **205** according to GP-1 with a modified work-up: the crude product, obtained after washing the organic layer with 2 N HCl and evaporation of the solvent, was purified by column chromatography (pentane:EtOAc, 2:1 followed by CH_2Cl_2:Et_2O, 1:1 +1% AcOH) to give the hemiester **206** in 79% yield (218 mg, 0.789 mmol) as a white solid.

Mp: 135 °C (rac), 126 °C (en), lit.[270] mp: 122-124 °C (rac).
$[\alpha]^{rt}_D$ = −10.8 (c = 1.00, MeOH).
ee = 96% [GC-analysis of the lactone: Lipodex E, t_1 = 95.9, t_2 = 98.7 (major)].
^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.42-1.48 (m, 2H), 1.70-1.78 (m, 2H), 2.94/2.97 (AB-system, *J* = 9.4 Hz, 2H), 4.81-4.89 (m, 2H), 4.94/5.06 (AB-system, *J* = 12.4 Hz, 2H), 7.21-7.30 (m, 5H), 8.20 (br s, 1H).
^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.3, 52.5, 52.6, 67.3, 78.7, 78.9, 128.5, 128.6, 128.8, 135.7, 170.8, 176.5.
IR (KBr): 2982, 1736, 1681, 1332, 1301, 1196, 1001 cm^{-1}.

EI-MS: m/z = 276 (M^+, 1), 258 (9), 169 (10), 141 (5), 123 (25), 108 (77), 91 (100), 79 (18), 68 (19), 65 (15).

Elemental Analysis for $C_{15}H_{16}O_5$ (276.28): Calcd.: C 65.21; H 5.84.
Found: C 65.32; H 5.96.

5.2.28 Synthesis of (2*R*,3*S*)-3-*exo*-benzyloxycarbonyl-7-oxabicyclo[2.2.1] heptane-2-*exo*-carboxylic acid (*ent*-206)

The product was obtained analogously to **5.2.27** from the quinine opening of anhydride **205** in 85% yield (234 mg, 0.847 mmol) as a white solid.

$[\alpha]^{rt}_D$ = +10.5 (c = 1.05, MeOH).
ee = 90% [GC-analysis of the lactone: Lipodex E, t_1 = 95.9 (major), t_2 = 98.7].

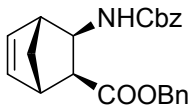
5.3 Synthesis of β-amino acids

5.3.1 General procedure for the preparation of *N*-Cbz protected amino acid benzyl esters (GP-2)

Ethyl chloroformate (2.86 mL, 30.00 mmol) was added to a mixture of the appropriate monoester (15.00 mmol) and Et_3N (6.27 mL, 45.00 mmol) in dry THF (25.0 mL) at –20 °C under argon. The reaction mixture was stirred at this temperature for 1 h. An aqueous solution of NaN_3 (2.93 g, 45.00 mmol; in 18.0 mL water) was added at –10 °C. The temperature was gradually increased to r.t. and stirring was continued for 2 h. The mixture was diluted with water, extracted with ethyl acetate and the organic phase was washed with aq. $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated providing the corresponding acyl azide. The crude acyl azide was dissolved in anhydrous benzene (18.0 mL) and heated under reflux for 2 h. After removal of benzene, benzyl alcohol (1.55 mL, 15.00 mmol) and Et_3N (4.18 mL, 30.00 mmol)

were added to a solution of the isocyanate in dry CH_2Cl_2 (20.0 mL). The reaction mixture was heated under reflux for 4 h. Evaporation of the solvent delivered an oily residue which was purified by column chromatography providing the corresponding *N*-protected amino acid benzyl ester.

5.3.2 Synthesis of (2*S*,3*R*)-3-*exo*-benzyloxycarbonylamino-bicyclo[2.2.1]hept-5-ene-2-*exo*-carboxylic acid benzyl ester (207)



The product was synthesized according to GP-2 by reaction of dicarboxylic acid monoester **202** (3.72 g, 13.66 mmol) with benzyl alcohol. The crude reaction product was purified by flash chromatography (petroleum ether:EtOAc, 4:1) delivering **207** in 72% yield (3.73 g, 9.88 mmol) as a white solid.

Mp: 44 °C (en).

$[\alpha]^{rt}_D$ = +17.4 (*c* = 2.63, $CHCl_3$).

ee = 93% [HPLC-analysis: Chiralpak AD at r.t., *n*-heptane:2-propanol = 94:6, 0.5 mL/min, 254 nm, t_1 = 30.1 min, t_2 = 46.8 min (major)].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.57 (dt, *J* = 1.7, 9.4 Hz, 1H), 1.97 (d, *J* = 9.4 Hz, 1H), 2.69 (d, *J* = 8.4 Hz, 1H), 2.73 (br s, 1H), 2.95 (br s, 1H), 4.03 (t, *J* = 8.4 Hz, 1H), 4.95-5.13 (m, 4H), 5.52 (d, *J* = 9.6 Hz, 1H), 6.15-6.25 (m, 2H), 7.24-7.38 (m, 10H).

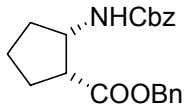
^{13}C NMR (75 MHz, $CDCl_3$): δ = 44.7, 46.2, 46.7, 48.8, 53.5, 66.8, 67.0, 128.3, 128.4, 128.5, 128.7, 128.8, 135.9, 136.8, 137.5, 138.7, 158.0, 174.3.

IR (KBr): 3352, 2978, 1718, 1529, 1337, 1267, 1252, 1235, 1189, 1032 cm^{-1}.

EI-MS: m/z = 353 (M^+, 1), 262 (9), 218 (39), 91 (100).

Elemental Analysis for $C_{23}H_{23}NO_4$ (377.43): Calcd.: C 73.19; H 6.14; N 3.71.
Found: C 73.20; H 6.16; N 3.77.

5.3.3 Synthesis of (1*R*,2*S*)-*cis*-2-benzyloxycarbonylamino-cyclopentane-1-carboxylic acid benzyl ester (208)



The product was synthesized according to GP-2 by reaction of dicarboxylic acid monoester *ent*-**193** (3.45 g, 13.90 mmol) with benzyl alcohol. The crude reaction product was purified by flash chromatography (pentane:EtOAc, 4:1) delivering **208** in 77% (3.78 g, 10.70 mmol) yield as a white solid.

Mp: 55 °C (rac), 77 °C (en).

$[\alpha]^{rt}_D$ = –41.1 (*c* = 1.83, $CHCl_3$).

ee = 94% (99.7% after recrystallization) [HPLC-analysis: Chiralpak AD at r.t., *n*-heptane:2-propanol = 90:10, 0.8 mL/min, 254 nm, t_1 = 14.9 min (major), t_2 = 19.2 min].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.55-1.85 (m, 3H), 1.89-2.03 (m, 3H), 3.05 (q, *J* = 7.2 Hz, 1H), 4.24-4.34 (m, 1H), 5.00/5.08 (AB-system, *J* = 18.3 Hz, 2H), 5.02/5.11 (AB-system, *J* = 12.4 Hz, 2H), 5.25 (d, *J* = 8.4 Hz, 1H), 7.26-7.39 (m, 10H).

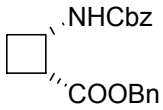
^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.1, 27.8, 32.1, 46.8, 54.3, 66.4, 66.6, 128.1, 128.2, 128.2, 128.5, 128.6, 135.8, 136.5, 155.8, 174.1.

IR (KBr): 3333, 2950, 1719, 1688, 1529, 1455, 1319, 1244, 1184, 1044 cm^{-1}.

EI-MS: m/z = 353 (M^+, 2), 262 (3), 218 (4), 156 (53), 138 (14), 107 (42), 91 (100).

Elemental Analysis for $C_{21}H_{23}NO_4$ (353.41): Calcd.: C 71.37; H 6.56; N 3.96.
Found: C 71.09; H 6.75; N 4.18.

5.3.4 Synthesis of (1*R*,2*S*)-*cis*-2-benzyloxycarbonylamino-cyclobutane-1-carboxylic acid benzyl ester (209)



The product was synthesized according to GP-2 by reaction of dicarboxylic acid monoester *ent*-**192** (3.28 g, 14.00 mmol) with benzyl alcohol. The crude reaction product was purified by flash chromatography (pentane:EtOAc, 6:1) delivering **209** in 74% yield (3.52 g, 10.37 mmol) as a colorless oil.

$[\alpha]^{rt}_D$ = –61.6 (c = 5.00, $CHCl_3$).

ee = 93% [HPLC-analysis: Chiralpak AD at r.t., *n*-heptane:2-PrOH = 95:5, 0.5 mL/min, 254 nm, t_1 = 38.9 min (major), t_2 = 45.0 min].

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.97-2.03 (m, 2H), 2.23-2.33 (m, 1H), 2.35-2.38 (m, 1H), 3.45 (s, 1H), 4.57 (p, *J* = 8.8 Hz, 1H), 5.02/5.08 (AB-system, *J* = 12.2 Hz, 2H), 5.10/5.16 (AB-system, *J* = 12.4 Hz, 2H), 5.69 (d, *J* = 8.8 Hz, 1H), 7.29-7.38 (m, 10H).

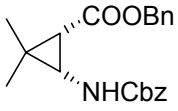
^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.0, 30.2, 45.6, 46.5, 66.7, 67.0, 128.3, 128.4, 128.5, 128.7, 128.8, 136.0, 136.6, 155.4, 174.2.

IR (capillary): 3350, 2952, 1724, 1515, 1334, 1251, 1213, 1169, 1049 cm^{-1}.

EI-MS: m/z = 311 (4), 220 (5), 204 (14), 177 (7), 132 (8), 107 (7), 91 (100).

Elemental Analysis for $C_{20}H_{21}NO_4$ (339.39): Calcd.: C 70.78; H 6.24; N 4.13.
Found: C 70.64; H 6.17; N 4.41.

5.3.5 Synthesis of (1*R*,2*S*)-*cis*-2-benzyloxycarbonylamino-3,3-dimethyl-cyclopropane-1-carboxylic acid benzyl ester (210)



The product was synthesized according to GP-2 by reaction of dicarboxylic acid monoester **190** (3.46 g, 13.94 mmol) with benzyl alcohol. The crude reaction product was purified by flash chromatography (pentane:EtOAc, 6:1) delivering **210** in 70% (3.47 g, 9.82 mmol) yield as a colorless oil.

$[\alpha]^{rt}_D$ = –7.3 (c = 5.00, $CHCl_3$).

ee = 19% [HPLC-analysis: Chiralpak AD at r.t., *n*-heptane:2-PrOH = 94:6, 0.7 mL/min, 254 nm, t_1 = 17.8 min, t_2 = 21.3 min (major)].

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.13 (s, 3H), 1.20 (s, 3H), 1.69 (d, *J* = 7.7 Hz, 1H), 3.20 (t, *J* = 7.4 Hz, 1H), 5.08-5.14(m, 4H), 6.26 (d, *J* = 6.0 Hz, 1H), 7.27-7.37 (m, 10H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.5, 26.2, 26.6, 27.9, 41.5, 66.8, 67.1, 128.3, 128.5, 128.6, 128.7, 128.8, 136.0, 136.8, 157.1, 171.5.

IR (capillary): 3401, 2957, 1725, 1510, 1344, 1221, 1154, 1065 cm^{-1}.

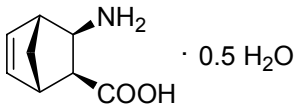
EI-MS: m/z = 353 (M^+, 1), 262 (9), 218 (39), 91 (100).

Elemental Analysis for $C_{21}H_{23}NO_4$ (353.41): Calcd.: C 71.37; H 6.56; N 3.96.
Found: C 71.46; H 6.92; N 4.01.

5.3.6 General procedure for the synthesis of the deprotected *β*-amino acids (GP-3)

A solution of the *N*-protected *β*-amino acid benzyl ester in dry MeOH (4.0 mL/mmol) was hydrogenated over 10% Pd/C for 1-2 h at r.t. and at 1 atm. The complete conversion of the reaction was monitored by t.l.c., the catalyst was removed by filtration through Celite, washed with MeOH and the filtrate was evaporated to give the corresponding free amino acid.

5.3.7 Synthesis of (2*S*,3*R*)-3-*exo*-amino-bicyclo[2.2.1]heptane-2-*exo*-carboxylic acid (214)



The product was synthesized from β-amino ester **207** (1.68 g, 4.45 mmol) according to GP-3 in 97% yield (709 mg, 4.32 mmol) as a white solid.

Mp: (dec) >250 °C (rac), (dec) >250 °C (en), lit.[271] mp: 275-278 °C (rac), lit.[223] mp: 198-207 °C (en, 214·HCl).

$[\alpha]^{rt}_D$ = –8.0 (*c* = 1.40, H_2O), lit.[223] $[\alpha]^{rt}_D$ (214·HCl) = –3.8 (*c* = 0.30, MeOH).

^{1}H NMR (300 MHz, D_2O): δ = 1.16-1.18 (m, 2H), 1.23 (d, *J* = 10.9 Hz, 1H), 1.43-1.60 (m, 2H), 1.66 (d, *J* = 10.9 Hz, 1H), 2.30 (s, 1H), 2.42 (s, 1H), 2.53 (d, *J* = 7.9 Hz, 1H), 3.30 (d, *J* = 7.9 Hz, 1H).

^{13}C NMR (75 MHz, D_2O): δ = 25.8, 28.0, 33.5, 41.1, 41.9, 51.3, 54.7, 178.9.

IR (KBr): 3424, 2955, 2676, 1632, 1537, 1395, 1367, 1316 cm^{-1}.

EI-MS: m/z = 155 (M^+, 70), 138 (13), 127 (52), 110 (43), 82 (45), 70 (100), 56 (90).

Elemental Analysis for $C_8H_{13}NO_2 \cdot 0.5H_2O$ (164.20):

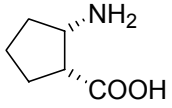
Calcd.: C 58.52; H 8.59; N 8.53.

Found: C 58.24; H 8.36; N 8.40.

HRMS for $C_8H_{13}NO_2$: Calcd.: 155.094629.

Found: 155.094568.

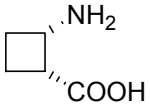
5.3.8 Synthesis of (1*R*,2*S*)-*cis*-2-amino-cyclopentane-1-carboxylic acid (213)



The product was synthesized from β-amino ester **208** (1.59 g, 4.50 mmol) according to GP-3 in 98% yield (570 mg, 4.41 mmol) as a white solid.

Mp: (dec) 194 °C (rac), (dec) 192 °C (en), lit.[219b] mp: 194-197 °C (en).
$[\alpha]^{rt}_D$ = –10.1 (*c* = 2.81, H_2O), lit.[272] $[\alpha]^{rt}_D$ = –9.6 (*c* = 1.00, H_2O).
^{1}H NMR (300 MHz, D_2O): δ = 1.52-1.74 (m, 4H), 1.86-2.00 (m, 2H), 2.71 (dt, *J* = 6.4, 8.4 Hz, 1H), 3.56 (dt, *J* = 4.2, 6.4 Hz, 1H).
^{13}C NMR (75 MHz, D_2O): δ = 21.3, 28.0, 29.5, 47.6, 53.0, 180.8.
IR (KBr): 3420, 2955, 1627, 1577, 1506, 1461, 1440, 1411, 1311, 1122, 1073 cm^{-1}.
EI-MS: m/z = 129 (M^+, 12), 100 (8), 82 (7), 69 (7), 56 (100).
Elemental Analysis for $C_6H_{11}NO_2$ (129.16): Calcd.: C 55.80; H 8.58; N 10.84.
Found: C 55.52; H 8.46; N 11.19.

5.3.9 Synthesis of (1*R*,2*S*)-*cis*-2-amino-cyclobutane-1-carboxylic acid (212)



The product was synthesized from β-amino ester **209** (1.02 g, 4.35 mmol) according to GP-3 in 93% yield (466 mg, 4.05 mmol) as a white solid.

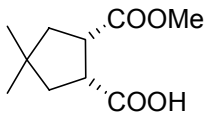
Mp: (dec) 130 °C (en), lit.[273] mp: (dec) 129-132 °C (rac), lit.[213] mp: (dec) 130 °C (en).
$[\alpha]^{rt}_D$ = –80.0 (*c* = 1.00, H_2O), lit.[216] $[\alpha]^{rt}_D$ = –70.0 (*c* = 1.03, H_2O).
^{1}H NMR (300 MHz, D_2O): δ = 1.90-2.00 (m, 1H), 2.07-2.30 (m, 3H), 3.09-3.17 (m, 1H), 3.79-3.86 (m, 1H).
^{13}C NMR (75 MHz, D_2O): δ = 21.1, 25.0, 41.3, 45.5, 181.0.
IR (KBr): 3433, 2956, 2190, 1541, 1405, 1293 cm^{-1}.
MS (FAB): 114 (M^+-H).
Elemental Analysis for $C_5H_9NO_2$ (115.13): Calcd.: C 52.16; H 7.88; N 12.17.
Found: C 51.80; H 7.97; N 11.81.

5.4 Synthesis of C_2-symmetric chiral bis(hydroxyamides)

5.4.1 General procedure for the alkaloid-mediated methanolysis of cyclic *meso*-anhydrides (GP-4)

Methanol (0.122 mL, 3.00 mmol) was added dropwise to a stirred suspension of the anhydride (1.00 mmol) and the alkaloid (0.357 g, 1.10 mmol) in a 1:1-mixture of toluene and tetrachloromethane (5.0 mL in the case of quinidine, 20.0 mL in the case of quinine) at –55 °C under argon. The reaction mixture was stirred at this temperature for 60 h. During this period the material gradually dissolved. Subsequently, the resulting clear solution was concentrated in vacuum to dryness and the resulting residue was dissolved in ethyl acetate (10.0 mL). The solution was washed with 2 N HCl (3 × 3.0 mL), followed by extraction of the aqueous phase with ethyl acetate (3 × 5.0 mL). The combined organic layer was dried over $MgSO_4$, filtered and concentrated to provide the corresponding hemiester.

5.4.2 Synthesis of (1*R*,2*S*)-*cis*-2-methoxycarbonyl-4,4-dimethylcyclopentane-1-carboxylic acid



The product was obtained according to GP-4 from the quinidine opening of anhydride **194** in 97% yield (195 mg, 0.974 mmol) as a colorless oil.

Mp: 52-53 °C (rac).

$[\alpha]^{rt}_D$ = +4.26 (c = 1.95, $CHCl_3$).

ee = 94% [GC-analysis of the lactone: Lipodex E, t_1 = 68.2, t_2 = 70.0 (major)].

^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.98 (s, 3H), 1.11 (s, 3H), 1.74-1.81 (m, 2H), 1.87-1.93 (m, 2H), 3.18-3.25 (m, 2H), 3.63 (s, 3H), 11.10 (br s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 29.1, 29.7, 38.9, 43.8, 46.3, 46.3, 52.0, 174.6, 180.8.

IR (KBr): 3038, 2961, 2875, 1741, 1699, 1474, 1448, 1421, 1320, 1287, 1230, 1208, 1161, 1044 cm^{-1}.

EI-MS: m/z = 182 (13), 169 (M^+-31, 36), 154 (45), 140 (31), 128 (55), 114 (47), 95 (100), 81 (29), 55 (26).

Elemental Analysis for $C_{10}H_{16}O_4$ (200.23): Calcd.: C 59.98; H 8.05.
Found: C 59.88; H 7.83.

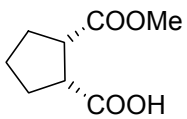
5.4.3 Synthesis of (1*S*,2*R*)-*cis*-2-methoxycarbonyl-4,4-dimethylcyclopentane-1-carboxylic acid

The product was obtained according to GP-4 from the quinine opening of anhydride **194** in 95% yield (190 mg, 0.949 mmol) as a colorless oil.

$[\alpha]^{rt}_D$ = –4.14 (c = 2.15, $CHCl_3$).

ee = 91% [GC-analysis of the lactone: Lipodex E, t_1 = 68.2(major), t_2 = 70.0].

5.4.4 Synthesis of (1*R*,2*S*)-*cis*-2-methoxycarbonyl-cyclopentane-1-carboxylic acid (219)



The product was obtained according to GP-4 from the quinidine opening of anhydride **177** in 95% yield (6.57 g, 38.16 mmol) as a colorless oil.

$[\alpha]^{rt}_D$ = +5.68 (*c* = 0.95, $CHCl_3$), $[\alpha]^{rt}_D$ = +8.3 (c = 2.1, MeOH), lit.[274] $[\alpha]^{rt}_D$ = +1.00 (*c* = 1.00, $CHCl_3$), lit.[275] $[\alpha]^{rt}_D$ = +5.00 (c = 1.40, MeOH).

ee = 96% [GC-analysis of the lactone: Lipodex E, t_1 = 68.6 (major), t_2 = 69.6].

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.62-1.70 (m, 1H), 1.86-2.10 (m, 5H), 3.05-3.12 (m, 2H), 3.67 (s, 3H), 11.45 (br s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.0, 28.8, 46.9, 47.0, 51.8, 174.3, 180.4.

IR (capillary): 2958, 2880, 1737, 1438, 1205 cm^{-1}.

EI-MS: m/z = 173 (M^++1, <2), 154 (35), 141 (M^+-31, 77), 126 (40), 113 (57), 95 (36), 67(100).

Elemental Analysis for $C_8H_{12}O_4$ (172.18): Calcd.: C 55.81; H 7.02.
Found: C 55.86; H 7.04.

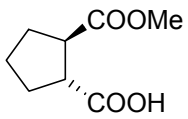
5.4.5 Synthesis of (1*S*,2*R*)-*cis*-2-methoxycarbonyl-cyclopentane-1-carboxylic acid (*ent*-219)

The product was obtained according to GP-4 from the quinine opening of anhydride **177** in 94% yield (3.23 g, 18.76 mmol) as a colorless oil.

$[\alpha]^{rt}_D$ = –8.0 (c = 2.67, MeOH).

ee = 93% [GC-analysis of the lactone: Lipodex E, t_1 = 68.6, t_2 = 69.6 (major)].

5.4.6 Synthesis of (1*R*,2*R*)-2-methoxycarbonyl-cyclopentane-1-carboxylic acid (232)



A freshly prepared LDA solution (3.0 eq.) in absolute THF (0.75 mL/mmol LDA) was added dropwise, over 1.5 h, to a stirred solution of the monomethylester **219** (5.165

g, 30.00 mmol) in absolute THF (45.0 mL) at –78 °C under argon. After the complete addition, the mixture was stirred at this temperature for 4 h, acidified with 4 N aq. HCl and extracted with ethylacetate. The combined organic phases were dried over $MgSO_4$, concentrated, and the residue was purified by column chromatography (pentane:Et_2O, 4:1) to yield 4.135 g (24.02 mmol, 80%) of the title compound as a colorless oil.

$[\alpha]^{rt}_D$ = –83.6 (c = 3.60, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.72-1.94 (m, 4H), 2.05-2.16 (m, 2H), 3.12-3.22 (m, 2H), 3.72 (s, 3H), 10.70 (br s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 25.3, 30.3, 30.6, 46.8, 47.0, 52.0, 175.1, 180.6.

IR (capillary): 2959, 2878, 1736, 1708, 1439, 1298, 1203 cm^{-1}.

EI-MS: m/z = 173 (M^++1, <2), 154 (43), 141 (M^+-31, 40), 126 (70), 112 (45), 95 (50), 67 (100), 55(15).

Elemental Analysis for $C_8H_{12}O_4$ (172.18): Calcd.: C 55.81; H 7.02.
Found: C 55.84; H 6.88.

5.4.7 Synthesis of (1*S*,2*S*)-2-methoxycarbonyl-cyclopentane-1-carboxylic acid (*ent*-232)

The product was prepared analogously to **5.4.6**, from the *cis* hemiester *ent*-**219** in 76% yield (2.035, 11.82 mmol).

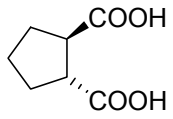
$[\alpha]^{rt}_D$ = +76.3 (c = 1.07, $CHCl_3$). lit.[276] $[\alpha]^{rt}_D$ = +84.0 (c = 0.60, MeOH).

5.4.8 General procedure for the ester hydrolyses (GP-5)

A solution of the corresponding methyl ester in MeOH (4.0 mL/mmol) was treated with NaOH (1N, 3.0 eq.) and stirred at r.t. for 4 h. The mixture was acidified with 2 N

HCl and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered, and concentrated to provide the desired product. The product obtained by this way was used in the next step without further purification.

5.4.9 Synthesis of (1*R*,2*R*)-cyclopentane-1,2-dicarboxylic acid (220)



It was synthesized from *trans* hemiester **232** (4.305 g, 25.00 mmol) according to GP-5. The product was obtained as a white solid in 97% yield (3.835 g, 24.25 mmol).

Mp: 184-185 °C.

$[\alpha]^{rt}_D$ = –75.7 (c = 0.65, acetone).

^{1}H NMR (400 MHz, Acetone-d^6): δ = 1.55-1.62 (m, 2H), 1.65-1.74 (m, 2H), 1.89-1.97 (m, 2H), 2.95-3.01 (m, 2H), 10.20 (br s, 2H).

^{13}C NMR (100 MHz, Acetone-d^6): δ = 25.5, 30.5, 47.0, 175.5.

IR (KBr): 2985, 2887, 2663, 1704, 1420, 1287, 1223 cm^{-1}.

EI-MS: m/z = 159 (M^++1, <2), 140 (41), 112 (100), 99(29), 95 (29), 86 (11), 67 (99), 55 (16).

Elemental Analysis for $C_7H_{10}O_4$ (158.15): Calcd. : C 53.16; H 6.37.
Found: C 53.17; H 6.41.

5.4.10 Synthesis of (1*S*,2*S*)-cyclopentane-1,2-dicarboxylic acid (*ent*-220)

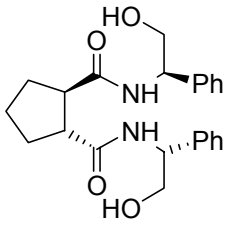
It was synthesized from *trans* hemiester *ent*-**232** (1.722 g, 10.00 mmol) according to GP-5. The product was obtained as a white solid in 95% yield (1.498 g, 9.47 mmol).

$[\alpha]^{rt}_D$ = +73.5 (c = 1.00, acetone).

5.4.11 General procedure for the synthesis of various C_2-symmetric bis(hydroxyamides) (GP-6)

Oxalyl chloride (2.56 mL, 30.00 mmol, 3.0 eq.) was added dropwise to a cooled suspension (0 °C) of the trans diacid (1.58 g, 10.00 mmol) and dimethylformamide (15%) in CH_2Cl_2 (50.0 mL) under argon. Gas evolution was accompanied by the formation of a clear, pale yellow solution which was stirred at r.t. for 1 h. The solvent and excess oxalyl chloride were removed in high vacuum, the solid residue was taken up in CH_2Cl_2 (40.0 mL) and added slowly, *via* syringe, to a cooled solution (0 °C) of the corresponding amino alcohol (22.00 mmol, 2.2 eq.) and Et_3N (6.93 mL, 50.00 mmol, 5.0 eq.) in CH_2Cl_2 (50.0 mL) under argon. Stirring was continued for 16 h at r.t., and it was accompanied by the formation of a white solid. The solid was filtered, washed with CH_2Cl_2 and dried in high vacuum to provide the corresponding bis(hydroxyamide).

5.4.12 Synthesis of (1*R*,2*R*)-cyclopentane-1,2-dicarboxylic acid bis-[(2'-hydroxy-1'-(*R*)-phenyl-ethyl)-amide] (221)



It was synthesized according to GP-6 on a 10.00 mmol scale by reaction of (1*R*,2*R*)-cyclopentane-dicarbonyl dichloride and (*R*)-phenylglycinol (3.018 g, 22.00 mmol, 2.2 eq.). The product was obtained in 62% yield (2.466 g, 6.22 mmol) as a white solid.

Mp: (dec) 240-243 °C.

$[\alpha]^{rt}_D$ = −162.5 (*c* = 1.00, DMSO).

^{1}H-NMR (400 MHz, CD_3OD): δ = 1.68-1.75 (m, 4H), 1.96-2.01 (m, 2H), 3.00-3.04 (m, 2H), 3.68 (dd, *J* = 7.7, 11.3 Hz, 2H), 3.73 (dd, *J* = 5.2, 11.3 Hz, 2H), 4.98 (dd, *J* = 5.2, 7.7 Hz, 2H), (3.68/3.73/4.98 ABX-system), 7.20-7.25 (m, 2H), 7.30 (d, *J* = 4.4 Hz, 8H).

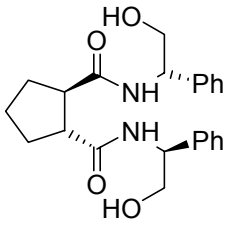
^{13}C-NMR (100 MHz, CD_3OD): δ = 25.5, 31.0, 49.2, 56.0, 65.1, 126.7, 127.1, 128.3, 140.0, 176.0.

IR (KBr): 3310, 2957, 1647, 1547, 1039 cm^{-1}.

EI-MS: m/z = 365 (M^+-31, 100), 260 (56), 233 (12), 167 (12), 140 (49), 121 (43), 106 (84), 95(14).

Elemental Analysis for $C_{23}H_{28}N_2O_4$ (396.48): Calcd.: C 69.67; H 7.12; N 7.07.
Found: C 69.43; H 7.13; N 7.03.

5.4.13 Synthesis of (1*R*,2*R*)-cyclopentane-1,2-dicarboxylic acid bis-[(2'-hydroxy-1'-(*S*)-phenyl-ethyl)-amide] (222)



It was synthesized according to GP-6 on a 10.00 mmol scale by reaction of (1*R*,2*R*)-cyclopentane-dicarbonyl dichloride and (*S*)-phenylglycinol (3.018 g, 22.00 mmol, 2.2 eq.). The product was isolated in 70% yield (2.780 g, 7.01 mmol) as a white solid.

Mp: (dec) 235-237 °C.

$[\alpha]^{rt}_D$ = +31.5 (*c* = 1.10, MeOH).

^{1}H-NMR (400 MHz, DMSO-d^6): δ = 1.58-1.71 (m, 4H), 1.91-1.97 (m, 2H), 2.92-2.98 (m, 2H), 3.47 (dd, *J* = 6.9, 11.0 Hz, 2H), 3.53 (dd, *J* = 5.8, 11.0 Hz, 2H), (3.47/3.53 AB part of an ABX-system), 4.79 (t, *J* = 5.8 Hz, 2H), 4.81 (q, *J* = 8.0 Hz, 2H), 7.16-7.23 (m, 10H), 8.02 (d, *J* = 8.2 Hz, 2H).

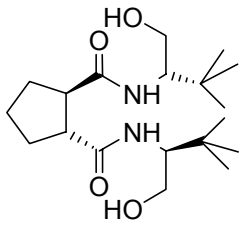
^{13}C-NMR (100 MHz, DMSO-d^6): δ = 25.3, 31.2, 47.5, 58.8, 64.5, 126.2, 126.5, 127.6, 140.9, 173.6.

IR (KBr): 3296, 3066, 2951, 2871, 1645, 1618, 1547, 1251, 1051 cm^{-1}.

EI-MS: m/z = 365 (M^+-31, 100), 260 (53), 233 (8), 167 (12), 140 (68), 121 (40), 106 (73), 95(15).

Elemental Analysis for $C_{23}H_{28}N_2O_4$ (396.48): Calcd.: C 69.67; H 7.12; N 7.07.
Found: C 69.71; H 7.40; N 6.95.

5.4.14 Synthesis of (1*R*,2*R*)-cyclopentane-1,2-dicarboxylic acid bis-[(2'-hydroxy-1'-(*S*)-*tert*-butyl-ethyl)-amide] (224)



It was synthesized according to GP-6 on a 10.00 mmol scale by reaction of (1*R*,2*R*)-cyclopentane-1,2-dicarbonyl dichloride and (*S*)-*tert*-leucinol (2.578 g, 22.00 mmol, 2.2 eq.). The product was isolated in 70% yield (2.511 g, 7.04 mmol) as a white solid.

Mp: 210-213 °C.

$[\alpha]^{rt}_D$ = –42.7 (*c* = 1.10, MeOH).

^{1}H-NMR (400 MHz, CD_3OD): δ = 0.90 (s, 18H), 1.71-1.85 (m, 4H), 2.06-2.12 (m, 2H), 3.00-3.07 (m, 2H), 3.44 (dd, *J* = 9.6, 12.1 Hz, 2H), 3.74-3.80 (m, 4H), 7.52 (d, *J* = 9.4 Hz, 2H).

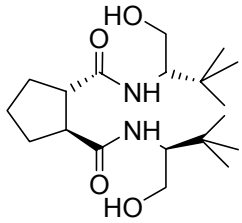
^{13}C-NMR (100 MHz, CD_3OD): δ = 25.5, 26.2, 31.6, 33.5, 49.1, 59.6, 61.2, 176.6.

IR (KBr): 3319, 2959, 2875, 1649, 1547, 1475, 1369, 1245, 1054 cm^{-1}.

EI-MS: m/z = 357 (M^++H, 3), 325 (M^+-31, 56), 299 (17), 281 (14), 263 (12), 240 (100), 222 (7), 212 (6), 194 (3), 140 (6), 100 (9), 86 (16).

Elemental Analysis for $C_{19}H_{36}N_2O_4$ (356.50): Calcd.:C 64.01; H 10.18; N 7.86.
Found: C 63.92; H 10.13; N 7.80.

5.4.15 Synthesis of (1*S*,2*S*)-cyclopentane-1,2-dicarboxylic acid bis-[(2'-hydroxy-1'-(*S*)-*tert*-butyl-ethyl)-amide] (225)



It was synthesized according to GP-6 on a 5.00 mmol scale by reaction of (1*S*,2*S*)-cyclopentane-1,2-dicarbonyl dichloride and (*S*)-*tert*-leucinol (1.289 g, 11.00 mmol, 2.2 eq.). The product was isolated in 65% yield (1.163 g, 3.26 mmol) as a white solid.

Mp: (dec) >250 °C.

$[\alpha]^{rt}_D$ = +76.6 (*c* = 0.50, MeOH).

^{1}H-NMR (300 MHz, CD_3OD): δ = 0.95 (s, 9H), 1.77-2.08 (m, 6H), 2.95-3.04 (m, 2H), 3.40-3.48 (m, 2H), 3.78-3.86 (m, 4H).

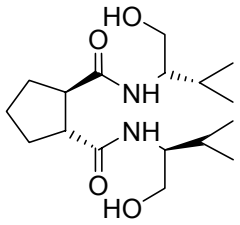
^{13}C-NMR (75 MHz, CD_3OD): δ = 25.6, 25.8, 30.6, 33.2, 49.4, 59.6, 60.7, 176.8.

IR (KBr): 3291, 2957, 2871, 1640, 1555, 1461, 1397, 1368, 1249, 1050, 1023 cm^{-1}.

EI-MS: m/z = 357 (M^++H, 7), 325 (M^+-31, 53), 299 (15), 281 (14), 263 (21), 240 (100), 222 (11), 212 (7), 194 (6), 140 (8), 100 (8), 86 (15).

Elemental Analysis for $C_{19}H_{36}N_2O_4$ (356.50): Calcd.: C 64.01; H 10.18; N 7.86.
Found: C 63.70; H 10.41; N 7.60.

5.4.16 Synthesis of (1*R*,2*R*)-cyclopentane-1,2-dicarboxylic acid bis-[(2'-hydroxy-1'-(*S*)-isopropyl-ethyl)-amide] (223)



It was synthesized according to GP-6 on a 5.00 mmol scale by reaction of (1*R*,2*R*)-cyclopentane-1,2-dicarbonyl dichloride and (*S*)-valinol (1.135 g, 11.00 mmol, 2.2 eq.). The product was isolated in 70% yield (1.157 g, 3.52 mmol) as a white solid.

Mp: 242 °C.

$[\alpha]^{rt}_D$ = +32.3 (*c* = 0.60, MeOH).

^{1}H-NMR (400 MHz, CD_3OD): δ = 0.85 (d, *J* = 6.9 Hz, 6H), 0.89 (d, *J* = 6.6 Hz, 6H), 1.70-1.87 (m, 6H), 1.98-2.06 (m, 2H), 2.92-2.99 (m, 2H), 3.51 (dd, *J* = 6.3, 11.3 Hz, 2H), 3.55 (dd, *J* = 4.7, 11.3 Hz, 2H), (3.51/3.55 AB part of an ABX-system), 3.65 (td, *J* = 4.7, 6.3 Hz, 2H).

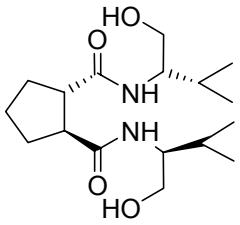
^{13}C-NMR (100 MHz, CD_3OD): δ = 17.7, 18.8, 25.1, 28.6, 31.3, 49.1, 56.6, 61.7, 175.9.

IR (KBr): 3305, 2958, 2873, 1637, 1545, 1243, 1073 cm^{-1}.

EI-MS: m/z = 297 (M^+-31, 64), 279 (17), 226 (100), 208 (8), 198 (6), 140 (5), 104 (8), 95 (12), 86 (21).

HRMS for $C_{17}H_{32}N_2O_4$-CH_2OH^+: Calcd.: 297.217818.
Found: 297.217839.

5.4.17 Synthesis of (1*S*,2*S*)-cyclopentane-1,2-dicarboxylic acid bis-[(2'-hydroxy-1'-(*S*)-isopropyl-ethyl)-amide] (226)



It was synthesized according to GP-6 on a 5.00 mmol scale by reaction of (1*S*,2*S*)-cyclopentane-1,2-dicarbonyl dichloride and (*S*)-valinol (1.135 g, 11.00 mmol, 2.2 eq.). The product was isolated in 66% yield (1.089 g, 3.31 mmol) as a white solid.

Mp: 225.5-226 °C.

$[\alpha]^{rt}_D$ = +32.3 (*c* = 0.60, MeOH).

^{1}H-NMR (400 MHz, CD_3OD): δ = 0.91 (d, *J* = 6.8 Hz, 6H), 0.95 (d, *J* = 6.6 Hz, 6H), 1.80-1.89 (m, 6H), 2.02-2.04 (m, 2H), 2.95-2.98 (m, 2H), 3.52 (dd, *J* = 6.6, 11.3 Hz, 2H), 3.61 (dd, *J* = 4.1, 11.3 Hz, 2H), (3.52/3.61 AB part of an ABX-system), 3.69-3.73 (m, 2H).

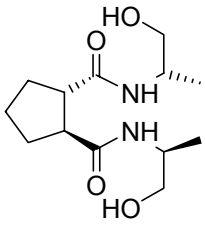
^{13}C-NMR (100 MHz, CD_3OD): δ = 17.6, 18.8, 25.4, 28.8, 30.9, 49.2, 56.7, 61.9, 176.1.

IR (KBr): 3274, 2952, 2873, 1638, 1556, 1245, 1074 cm^{-1}.

EI-MS: m/z = 297 (M^+-31, 61), 279 (19), 226 (100), 208 (9), 198 (8), 180 (4), 168 (7), 140 (6), 130 (5), 95 (12).

Elemental Analysis for $C_{17}H_{32}N_2O_4$ (328.45): Calcd.: C 62.17; H 9.82; N 8.53.
Found: C 62.07; H 9.94; N 8.43.

5.4.18 Synthesis of (1*S*,2*S*)-cyclopentane-1,2-dicarboxylic acid bis-[(2'-hydroxy-1'-(*S*)-methyl-ethyl)-amide] (227)



It was synthesized according to GP-6 on a 5.00 mmol scale by reaction of (1*S*,2*S*)-cyclopentane-1,2-dicarbonyl dichloride and (*S*)-alaninol (0.826 g, 11.00 mmol, 2.2 eq.). The product was isolated in 74% yield (1.014 g, 3.72 mmol) as a white solid.

Mp: 213-215 °C.

$[\alpha]^{rt}_D$ = +51.5 (*c* = 0.27, MeOH).

^{1}H-NMR (400 MHz, CD_3OD): δ = 1.12 (d, *J* = 6.6 Hz, 6H), 1.74-1.82 (m, 4H), 1.94-2.04 (m, 2H), 2.83-2.90 (m, 2H), 3.45 (dd, *J* = 5.7, 11.0 Hz, 2H), 3.48 (dd, *J* = 5.2, 11.0 Hz, 2H), (3.45/3.48 AB part of an ABX-system), 3.91-3.99 (m, 2H).

^{13}C-NMR (100 MHz, CD_3OD): δ = 15.8, 25.3, 30.7, 48.3, 49.3, 64.9, 175.5.

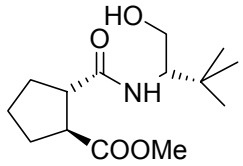
IR (KBr): 3281, 2972, 2950, 1633, 1550, 1250, 1087, 1052 cm^{-1}.

EI-MS: m/z = 273 (M^++1, 8), 241 (M^+-31, 58), 198 (100), 180 (21), 170 (8), 152 (4), 140 (9), 102 (12), 95 (11).

Elemental Analysis for $C_{13}H_{24}N_2O_4$ (272.34): Calcd.: C 57.33; H 8.88; N 10.29.
Found: C 57.16; H 9.17; N 10.33.

5.5. Synthesis of C_1-symmetric chiral bis(hydroxyamides)

5.5.1 Synthesis of (1*S*,2*S*)-2-[2'-hydroxy-1'-(*S*)-*tert*-butyl-ethylcarbamoyl]-cyclopentane-1-carboxylic acid methyl ester (233)



Oxalyl chloride (3.55 mL, 42.00 mmol, 1.5 eq.) was added dropwise with gas evolution to a cooled solution (0 °C, ice bath) of the *trans* hemiester *ent*-**232** (4.821 g, 28.00 mmol) and dimethylformamide (7%) in CH_2Cl_2 (112.0 mL) under argon. The reaction mixture was stirred for 1 h at r.t., followed by removal of the solvent and excess oxalyl chloride in high vacuum. The residue was taken up in CH_2Cl_2 (90.0 mL) and added *via* syringe to a cooled solution (0 °C) of (*S*)-*tert*-leucinol (3.610 g, 30.80 mmol, 1.1 eq.) and Et_3N (9.7 mL, 70.00 mmol, 2.5 eq.) in CH_2Cl_2 (112.0 mL) under argon. After stirring at r.t. overnight, the reaction mixture was acidified with 2 N HCl and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and concentrated to give the crude product as a yellow solid. Purification by column chromatography (pentane:EtOAc, 1:2) yielded 6.582 g (24.26 mmol, 87 % yield) of the title compound as a white solid.

Mp: 137-138 °C.

$[\alpha]^{rt}_D$ = +36.1 (*c* = 1.00, $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.96 (s, 9H), 1.67-1.86 (m, 3H), 1.91-2.01 (m, 2H), 2.07-2.15 (m, 1H), 2.70 (br s, 1H), 2.88 (q, *J* = 8.8 Hz, 1H), 3.10 (q, *J* = 8.8 Hz, 1H), 3.52 (dt, *J* = 3.0, 9.1 Hz, 1H), 3.71 (s, 3H), 3.80-3.85 (m, 2H), 6.16 (d, *J* = 8.5 Hz, 1H).

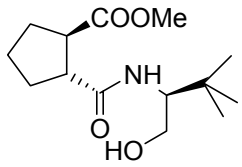
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 25.1, 26.8, 29.8, 30.0, 33.3, 48.3, 48.8, 52.1, 59.8, 63.0, 175.3, 176.1.

IR (KBr): 3304, 3248, 3086, 2873, 1734, 1636, 1567, 1432, 1356, 1193, 1174, 1055 cm^{-1}.

EI-MS: m/z = 272 (M^++H, 7), 240 (100), 214 (22), 196 (13), 182 (7), 155 (29), 127 (7), 95 (21), 86 (70), 67 (19).

Elemental Analysis for $C_{14}H_{25}NO_4$ (271.35): Calcd.: C 61.97; H 9.29; N 5.16. Found: C 62.05; H 9.05; N 5.04.

5.5.2 Synthesis of (1*R*,2*R*)-2-[2'-hydroxy-1'-(*S*)-*tert*-butyl-ethylcarbamoyl]-cyclopentane-1-carboxylic acid methyl ester (239)



Oxalyl chloride (1.02 mL, 12.0 mmol, 1.5 eq.) was added dropwise with gas evolution to a cooled solution (0 °C, ice bath) of the *trans* hemiester **232** (1.378 g, 8.00 mmol) and dimethylformamide (7%) in CH_2Cl_2 (32.0 mL) under argon. The reaction mixture was stirred for 1 h at r.t., followed by removal of the solvent and excess oxalyl chloride in high vacuum. The residue was taken up in CH_2Cl_2 (24.0 mL) and added *via* syringe to a cooled solution (0 °C) of (*S*)-*tert*-leucinol (1.031 g, 8.80 mmol, 1.1 eq.) and Et_3N (2.77 mL, 20.00 mmol, 2.5 eq.) in CH_2Cl_2 (32.0 mL) under argon. After stirring at r.t. overnight, the reaction mixture was acidified with 2 N HCl and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and concentrated to give the crude product as a yellow solid. Purification by column chromatography (pentane:EtOAc, 1:2) yielded 1.772 g (6.53 mmol, 82% yield) of the title compound as a white solid.

Mp: 101-102 °C.

$[\alpha]^{rt}_D$ = –68.2 (*c* = 1.00, $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.94 (s, 9H), 1.69-1.97 (m, 4H), 2.00-2.13 (m, 2H), 2.60 (br s, 1H), 2.90-3.02 (m, 2H), 3.54 (dd, *J* = 8.0, 10.7 Hz, 1H), 3.71 (s, 3H), 3.80-3.88 (m, 2H), 6.18 (d, *J* = 8.2 Hz, 1H).

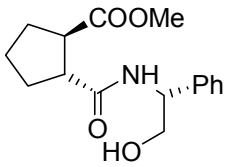
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 25.3, 26.8, 29.4, 30.6, 33.4, 48.5, 48.5, 52.0, 59.8, 63.4, 175.3, 175.9.

IR (KBr): 3266, 2957, 2873, 1741, 1642, 1568, 1442, 1348, 1267, 1234, 1200, 1143, 1054 cm^{-1}.

EI-MS: m/z = 272 (M^++H, 24), 240 (M^+-31, 100), 214 (24), 196 (18), 182 (10), 155 (28), 127 (9), 95 (25), 86 (83), 67 (23).

Elemental Analysis for $C_{14}H_{25}NO_4$ (271.35): Calcd.: C 61.97; H 9.29; N 5.16.
Found: C 61.80; H 9.46; N 4.98.

5.5.3 Synthesis of (1*R*,2*R*)-2-[2'-hydroxy-1'-(*R*)-phenyl-ethylcarbamoyl]-cyclopentane-1-carboxylic acid methyl ester (242)



Oxalyl chloride (2.54 mL, 30.00 mmol, 1.5 eq.) was added dropwise with gas evolution to a cooled solution (0 °C, ice bath) of the *trans* hemiester **232** (3.444 g, 20.00 mmol) and dimethylformamide (7%) in CH_2Cl_2 (80.0 mL) under argon. The reaction mixture was stirred for 1 h at r.t., followed by removal of the solvent and excess oxalyl chloride in high vacuum. The residue was taken up in CH_2Cl_2 (60.0 mL) and added *via* syringe to a cooled solution (0 °C) of (*R*)-phenylglycinol (3.018 g, 22.00 mmol, 1.1 eq.) and Et_3N (6.93 mL, 50.00 mmol, 2.5 eq.) in CH_2Cl_2 (80.0 mL) under argon. After stirring at r.t. overnight, the reaction mixture was acidified with 2 N HCl and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and concentrated to give the crude product as a yellow solid. Purification by column chromatography (pentane:EtOAc, 1:2) yielded 4.667 g (16.02 mmol, 80 % yield) of the title compound as a white solid.

Mp: 101-102 °C.

$[\alpha]^{rt}_D$ = –84.0 (*c* = 1.10, $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.58-1.90 (m, 2H), 1.98-2.07 (m, 2H), 2.84 (q, *J* = 8.5 Hz, 1H), 3.01(t, *J* = 5.5 Hz, 1H), 3.05 (q, *J* = 8.5 Hz, 1H), 3.63 (s, 3H), 3.71-3.77 (m, 2H), 4.98 (dt, *J* = 4.4, 7.2 Hz, 1H), 6.64 (d, *J* = 7.2 Hz, 1H), 7.19-7.30 (m, 5H).

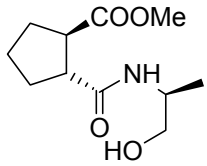
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 25.4, 30.2, 30.4, 48.2, 48.7, 52.2, 56.0, 66.6, 126.7, 127.8, 128.8, 139.1, 174.7, 176.1.

IR (KBr): 3255, 3081, 3031, 2956, 1731, 1638, 1570, 1453, 1439, 1257, 1199, 1172, 1083, 1047 cm^{-1}.

EI-MS: m/z = 260 (M^+-31, 74); 200 (3), 155 (8), 127 (4), 120 (6), 106 (100), 95 (17), 67 (17).

Elemental Analysis for $C_{16}H_{21}NO_4$ (291.34): Calcd.: C 65.96; H 7.27; N 4.81.
Found: C 65.95; H 7.04; N 4.81.

5.5.4 Synthesis of (1*R*,2*R*)-2-[2'-hydroxy-1'-(*S*)-methyl-ethylcarbamoyl]-cyclopentane-1-carboxylic acid methyl ester (245)



Oxalyl chloride (1.02 mL, 12.00 mmol, 1.5 eq.) was added dropwise with gas evolution to a cooled solution (0 °C, ice bath) of the *trans* hemiester **232** (1.378 g, 8.00 mmol) and dimethylformamide (7%) in CH_2Cl_2 (32.0 mL) under argon. The reaction mixture was stirred for 1 h at r.t., followed by removal of the solvent and excess oxalyl chloride in high vacuum. The residue was taken up in CH_2Cl_2 (24.0 mL) and added via syringe to a cooled solution (0 °C) of (*S*)-alaninol (0.661 g, 8.80 mmol, 1.1 eq.) and Et_3N (2.77 mL, 20.00 mmol, 2.5 eq.) in CH_2Cl_2 (32.0 mL) under argon.
After stirring at r.t. overnight, the reaction mixture was acidified with 2 N HCl and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and concentrated to give the crude product as a yellow solid.

Purification by column chromatography (pentane:EtOAc, 1:2) yielded 1.512 g (6.59 mmol, 82% yield) of the title compound as a white solid.

Mp: 83.5-84.5 °C.

$[\alpha]^{rt}_D$ = –74.6 (*c* = 0.82, $CHCl_3$).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.16 (d, *J* = 6.9 Hz, 3H), 1.64-1.84 (m, 3H), 1.89-1.97 (m, 2H), 2.04-2.16 (m, 1H), 2.85 (q, *J* = 8.6 Hz, 1H), 3.04 (q, *J* = 8.6 Hz, 1H), 3.13 (br s, 1H), 3.53 (dd, *J* = 6.0, 10.9 Hz, 1H), 3.64 (dd, *J* = 3.7, 10.9 Hz, 1H), (3.53/3.64 AB part of an ABX-system), 3.70 (s, 3H), 4.04 (qdd, *J* = 3.7, 6.7, 13.6 Hz, 1H), 6.20 (d, *J* = 6.2 Hz, 1H).

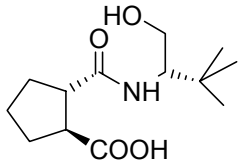
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 17.0, 25.4, 30.1, 30.5, 47.9, 48.0, 48.5, 52.0, 175.1, 176.1.

IR (KBr): 3272, 2958, 1734, 1642, 1558, 1447, 1392, 1240, 1203, 1044 cm^{-1}.

EI-MS: m/z = 230 (M^++1, 26), 198 (M^+-31, 100), 155 (81), 127 (13), 95 (39), 67 (35).

Elemental Analysis for $C_{11}H_{19}NO_4$ (229.27): Calcd.: C: 57.62; H: 8.35; N: 6.11.
Found: C: 57.49; H: 8.30; N: 5.97.

5.5.5 Synthesis of (1*S*,2*S*)-2-[2'-hydroxy-1'-(*S*)-*tert*-butyl-ethylcarbamoyl]-cyclopentane-1-carboxylic acid (235)



The title compound was synthesized from **233** (3.528 g, 13.00 mmol) according to GP-5. The product was obtained as a white solid in 95% yield (3.177 g, 12.34 mmol).

Mp: 147 °C.

$[\alpha]^{rt}_D$ = +46.5 (*c* = 1.03, acetone).

^{1}H-NMR (400 MHz, Acetone-d^6): δ = 0.92 (s, 9H), 1.60-1.75 (m, 2H), 1.77-1.89 (m, 2H), 1.94-2.06 (m, 2H), 2.98 (q, *J* = 8.5 Hz, 1H), 3.10 (q, *J* = 8.5 Hz, 1H), 3.51 (dd, *J* = 8.0, 11.3 Hz, 1H), 3.70 (dd, *J* = 3.8, 11.3 Hz, 1H), (3.51/3.70 AB part of an ABX-system), 3.81 (ddd, *J* = 3.8, 8.0, 9.6 Hz, 1H), 6.90 (br s, 1H).

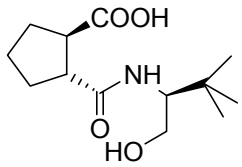
^{13}C-NMR (100 MHz, Acetone-d^6): δ = 25.1, 26.5, 29.6, 31.0, 33.7, 47.1, 48.6, 59.4, 61.6, 174.9, 175.6.

IR (KBr): 3244, 3088, 2961, 2872, 1701, 1637, 1569, 1369, 1295, 1250, 1054 cm^{-1}.

EI-MS: m/z = 226 (M^+-31, 86), 200 (34), 182 (16), 141 (13), 95 (21), 86 (100), 67 (22), 60 (58).

Elemental Analysis for $C_{13}H_{23}NO_4$ (257.33): Calcd.: C 60.68; H 9.01; N 5.44.
Found: C 60.32; H 8.77; N 5.45.

5.5.6 Synthesis of (1*R*,2*R*)-2-[2'-hydroxy-1'-(*S*)-*tert*-butyl-ethylcarbamoyl]-cyclopentane-1-carboxylic acid (240)



The title compound was synthesized from **239** (1.357 g, 5.00 mmol) according to GP-5. The product was obtained as a white solid in 98% yield (1.265 g, 4.92 mmol).

Mp: 134-135 °C.

$[\alpha]^{rt}_D$ = –55.9, (*c* = 0.56, acetone).

^{1}H-NMR (400 MHz, Acetone-d^6): δ = 0.94 (s, 9H), 1.63-2.10 (m, 6H), 3.00 (q, *J* = 8.2 Hz, 1H), 3.06 (q, *J* = 8.2 Hz, 1H), 3.55 (dd, *J* = 7.7, 11.3 Hz, 1H), 3.74 (dd, *J* = 3.8, 11.3 Hz, 1H), (3.55/3.74 AB part of an ABX-system), 3.82 (dd, *J* = 3.8, 7.7 Hz, 1H).

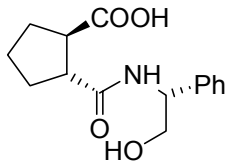
^{13}C-NMR (100 MHz, Acetone-d^6): δ = 26.0, 27.3, 30.9, 31.2, 34.5, 48.3, 49.3, 59.8, 62.2, 175.4, 176.3.

IR (KBr): 3462, 3287, 2960, 2876, 1710, 1619, 1585, 1473, 1424, 1395, 1246, 1222, 1057 cm^{-1}.

EI-MS: m/z = 258 (M^++1, 19), 226 (M^+-31, 91), 208 (11), 200 (30), 182 (17), 141 (10), 95 (18), 86 (100), 67 (22), 60 (57).

Elemental Analysis for $C_{13}H_{23}NO_4$ (257.33): Calcd.: C: 60.68; H: 9.01; N: 5.44.
Found: C: 60.42; H: 9.24; N: 5.25.

5.5.7 Synthesis of (1*R*,2*R*)-2-[2'-hydroxy-1'-(*R*)-phenyl-ethylcarbamoyl]-cyclopentane-1-carboxylic acid (243)



The title compound was synthesized from **242** (4.224 g, 14.50 mmol) according to GP-5. The product was obtained as a white solid in 97% yield (3.893 g, 14.04 mmol).

Mp: 133-134 °C.

$[\alpha]^{rt}_D$ = –96.9 (*c* = 1.00, acetone).

^{1}H-NMR (400 MHz, Acetone-d^6): δ = 1.58-1.79 (m, 3H), 1.82-1.90 (m, 1H), 1.96-2.09 (m, 2H), 3.07 (q, *J* = 8.0 Hz, 1H), 3.14 (q, *J* = 8.0 Hz, 1H), 3.74-3.78 (m, 2H), 5.02-5.07 (m, 1H), 7.21-7.40 (m, 5H), 7.58 (br s, 1H).

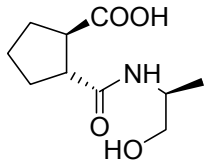
^{13}C-NMR (100 MHz, Acetone-d^6): δ = 26.0, 30.6, 31.6, 47.6, 49.1, 56.5, 66.2, 127.6, 127.6, 128.8, 141.7, 174.8, 176.2.

IR (KBr): 3302, 2956, 2870, 1701, 1652, 1548, 1452, 1387, 1301, 1270, 1051 cm^{-1}.

EI-MS: m/z = 246 (M^+-31, 61); 201 (5), 141 (4), 120 (7), 106 (100), 95 (11), 67 (12).

Elemental Analysis for $C_{15}H_{19}NO_4$ (277.32): Calcd.: C 64.95; H 6.91; N 5.05.
Found: C 64.57; H 6.89; N 4.94.

5.5.8 Synthesis of (1*R*,2*R*)-2-[2'-hydroxy-1'-(*S*)-methyl-ethylcarbamoyl]-cyclopentane-1-carboxylic acid (246)



The title compound was synthesized from **245** (1.146 g, 5.00 mmol) according to GP-5. The product was obtained as a white solid in 98% yield (1.053 g, 4.89 mmol).

Mp: 139.5-141 °C.

$[\alpha]^{rt}_D$ = –66.5 (*c* = 0.52, acetone).

^{1}H-NMR (400 MHz, Acetone-d^6): δ = 1.10 (d, *J* = 6.6 Hz, 3H), 1.60-2.02 (m, 6H), 2.91 (q, *J* = 8.2 Hz, 1H), 3.07 (q, *J* = 8.2 Hz, 1H), 3.45 (dd, *J* = 5.2, 10.7 Hz, 1H), 3.50 (dd, *J* = 5.5, 10.7 Hz, 1H), (3.45/3.50 AB part of an ABX-system), 3.92-3.99 (m, 1H).

^{13}C-NMR (100 MHz, Acetone-d^6): δ = 16.5, 25.3, 29.9, 30.9, 46.9, 47.3, 48.4, 65.4, 174.2, 175.3.

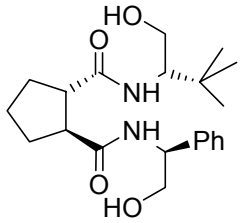
IR (KBr): 3303, 2975, 2871, 1712, 1646, 1562, 1451, 1293, 1235, 1202, 1098 cm^{-1}.

EI-MS: m/z = 216 (M^++1, 54), 198 (11), 184 (M^+-31, 100), 166 (4), 158 (5), 140 (13), 124 (4), 113 (8), 95 (42), 67 (49).

HRMS for $C_{10}H_{17}NO_4$: Calcd.: 215.115758.

Found: 215.115782.

5.5.9 Synthesis of (1*S*,2*S*)-cyclopentane-1,2-dicarboxylic acid 1-[(2'-hydroxy-1'-(*S*)-*tert*-butyl-ethyl)-amide]-2-[(2'-hydroxy-1'-(*S*)-phenyl-ethyl)-amide] (234)



Solid EEDQ (2.08 g, 8.40 mmol, 1.2 eq.) was added at 0 °C to a solution of **235** (1.80 g, 7.00 mmol) and (*S*)-phenylglycinol (0.960 g, 7.00 mmol, 1.0 eq.) in dry THF (70.0 mL) and the mixture was stirred at r.t. for 5 days. The solvent was removed in vacuum and the crude reaction product was purified by column chromatography (pentane:EtOAc, 1:1 + 5% MeOH) delivering the title compound in 83% yield (2.190 g, 5.82 mmol) as a white solid.

Mp: 185-188 °C.

$[\alpha]^{rt}_D$ = +117.2 (*c* = 1.00, MeOH).

^{1}H-NMR (400 MHz, CD_3OD): δ = 0.92 (s, 9H), 1.71-1.86 (m, 4H), 1.96-2.05 (m, 2H), 2.99 (q, *J* = 8.0 Hz, 1H), 3.05 (q, *J* = 8.0 Hz, 1H), 3.46 (dd, *J* = 8.8, 11.0 Hz, 1H), 3.66 (dd, *J* = 8.2, 11.5 Hz, 1H), 3.73 (dd, *J* = 5.0, 11.5 Hz, 1H), (3.66/3.73 AB part of an ABX-system), 3.77-3.84 (m, 2H), 5.01 (dd, *J* = 5.0, 8.2 Hz, 1H), 7.22-7.26 (m, 1H), 7.31 (d, *J* = 4.4 Hz, 4H).

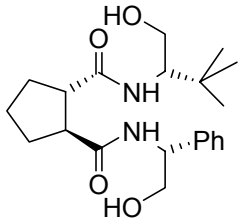
^{13}C-NMR (100 MHz, CD_3OD): δ = 25.6, 26.0, 30.5, 31.2, 33.4, 49.0, 49.5, 55.8, 59.6, 61.0, 64.9, 126.5, 127.0, 128.1, 139.8, 175.9, 176.5.

IR (KBr): 3291, 2959, 1640, 1553, 1249, 1050 cm^{-1}.

EI-MS: m/z = 345 (M^+-31, 100), 327 (7), 319 (13), 260 (40), 240 (76), 213 (14), 194 (8), 157 (8), 140 (41), 121 (23), 106 (52), 95 (18), 86 (23).

Elemental Analysis for $C_{21}H_{32}N_2O_4$ (376.49): Calcd.: C 66.99; H 8.57; N 7.44.
Found: C 66.96; H 8.58; N 7.26.

5.5.10 Synthesis of (1*S*,2*S*)-cyclopentane-1,2-dicarboxylic acid 1-[(2'-hydroxy-1'-(*S*)-*tert*-butyl-ethyl)-amide]-2-[(2'-hydroxy-1'-(*R*)-phenyl-ethyl)-amide] (238)



Solid EEDQ (2.08 g, 8.40 mmol, 1.2 eq.) was added at 0 °C to a solution of **235** (1.80 g, 7.00 mmol) and (*R*)-phenylglycinol (0.960 g, 7.00 mmol, 1.0 eq.) in dry THF (70.0 mL) and the mixture was stirred at r.t. for 5 days. The solvent was removed in vacuum and the crude reaction product was purified by column chromatography (pentane:EtOAc, 1:1 + 5% MeOH) delivering the title compound in 86% yield (2.281 g, 6.06 mmol) as a white solid.

Mp: 143.5-145 °C.

$[\alpha]^{rt}_D$ = +4.2 (*c* = 1.15, MeOH).

^{1}H-NMR (300 MHz, CD_3OD): δ = 0.90 (s, 9H), 1.71-1.91 (m, 4H), 1.99-2.13 (m, 2H), 2.97 (q, *J* = 8.2 Hz, 1H), 3.12 (q, *J* = 8.2 Hz, 1H), 3.38 (dd, *J* = 8.4, 11.4 Hz, 1H), 3.64-3.78 (m, 4H), 4.94 (dd, *J* = 5.4, 7.4 Hz, 1H), 7.20-7.27 (m, 1H), 7.31 (d, *J* = 4.4 Hz, 4H).

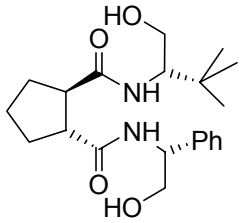
^{13}C-NMR (75 MHz, CD_3OD): δ = 25.1, 25.9, 30.6, 31.5, 33.4, 48.2, 48.9, 55.8, 59.3, 61.2, 64.8, 126.6, 126.8, 128.1, 139.8, 176.1, 176.2.

IR (KBr): 3308, 2960, 2873, 1646, 1544, 1457, 1368, 1244, 1049 cm^{-1}.

EI-MS: m/z = 345 (M^+-31, 100), 327 (8), 319 (13), 260 (36), 240 (69), 213 (8), 194 (6), 157 (8), 140 (50), 121 (26), 106 (42), 95 (18), 86 (22).

HRMS for $C_{21}H_{32}N_2O_4$-CH_2OH^+: Calcd.: 345.217817.
Found: 345.217812.

5.5.11 Synthesis of (1*R*,2*R*)-cyclopentane-1,2-dicarboxylic acid 1-[(2'-hydroxy-1'-(*S*)-*tert*-butyl-ethyl)-amide]-2-[(2'-hydroxy-1'-(*R*)-phenyl-ethyl)-amide] (244)



Solid EEDQ (2.08 g, 8.40 mmol, 1.2 eq.) was added at 0 °C to a solution of **243** (1.941 g, 7.00 mmol) and (*S*)-*tert*-leucinol (0.820 g, 7.00 mmol, 1.0 eq.) in dry THF (70.0 mL) and the mixture was stirred at r.t. for 5 days. The solvent was removed in vacuum and the crude reaction product was purified by column chromatography (pentane:EtOAc, 1:1 + 5% MeOH) delivering the title compound in 81% yield (2.131 g, 5.66 mmol) as a white solid.

Mp: 158-160 °C.

$[\alpha]^{rt}_D$ = −135.5 (*c* = 0.40, MeOH).

^{1}H-NMR (400 MHz, CD_3OD): δ = 0.94 (s, 9H), 1.62-1.92 (m, 4H), 1.99-2.12 (m, 2H), 2.97-3.09 (m, 2H), 3.48 (dd, *J* = 9.3, 12.1 Hz, 1H), 3.70 (dd, *J* = 6.3, 11.3 Hz, 1H), 3.73 (dd, *J* = 6.9, 11.3 Hz, 1H), (3.70/3.73 AB part of an ABX-system), 3.77-3.81 (m, 2H), 4.95 (t, *J* = 6.3 Hz, 1H), 7.24-7.32 (m, 1H), 7.33 (d, *J* = 4.4 Hz, 4H).

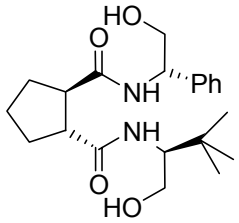
^{13}C-NMR (100 MHz, CD_3OD): δ = 24.9, 26.1, 30.3, 31.4, 33.5, 48.8, 49.6, 55.7, 59.4, 61.1, 64.8, 126.6, 126.9, 128.0, 140.0, 175.3, 176.2.

IR (KBr): 3275, 3083, 2960, 2872, 1635, 1554, 1455, 1368, 1351, 1243, 1051 cm^{-1}.

EI-MS: m/z = 345 (M^+-31, 100), 327 (8), 319 (14), 260 (39), 240 (74), 213 (12), 194 (9), 157 (8), 140 (42), 121 (29), 106 (53), 95 (19), 86 (20).

Elemental Analysis for $C_{21}H_{32}N_2O_4$ (376.49): Calcd.: C 66.99; H 8.57; N 7.44.
Found: C 66.88; H 8.42; N 7.34.

5.5.12 Synthesis of (1*R*,2*R*)-cyclopentane-1,2-dicarboxylic acid 1-[(2'-hydroxy-1'-(*S*)-*tert*-butyl-ethyl)-amide]-2-[(2'-hydroxy-1'-(*S*)-phenyl-ethyl)-amide] (241)



Solid EEDQ (1.19 g, 4.80 mmol, 1.2 eq.) was added at 0 °C to a solution of **240** (1.029 g, 4.00 mmol) and (*S*)-phenylglycinol (0.549 g, 4.00 mmol, 1.0 eq.) in dry THF (40.0 mL) and the mixture was stirred at r.t. for 5 days. The solvent was removed in vacuum and the crude reaction product was purified by column chromatography (pentane:EtOAc, 1:1 + 5% MeOH) delivering the title compound in 83% yield (1.250 g, 3.32 mmol) as a white solid.

Mp: 207 °C.

$[\alpha]^{rt}_D$ = +6.0 (*c* = 1.00, MeOH).

^{1}H-NMR (400 MHz, CD_3OD): δ = 0.74 (s, 9H), 1.75-1.92 (m, 4H), 1.99-2.07 (m, 1H), 2.11-2.18 (m, 1H), 2.96-3.05 (m, 2H), 3.36-3.43 (m, 1H), 3.69 (dd, *J* = 7.4, 11.3 Hz, 1H), 3.74 (dd, *J* = 5.5, 11.3 Hz, 1H), (3.69/3.74 AB part of an ABX-system), 3.68-3.74 (m, 2H), 4.99 (dd, *J* = 5.5, 7.4 Hz, 1H), 7.22-7.32 (m, 5H).

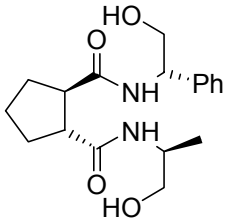
^{13}C-NMR (100 MHz, CD_3OD): δ = 25.2, 26.0, 30.6, 31.8, 33.3, 48.7, 49.6, 55.8, 59.4, 61.0, 64.9, 126.8, 126.9, 128.0, 139.8, 175.6, 176.1.

IR (KBr): 3317, 2961, 2872, 1623, 1540, 1368, 1253, 1086, 1049 cm^{-1}.

EI-MS: m/z = 377 (M^++1, 4), 345 (M^+-31, 100), 327 (9), 319 (14), 260 (29), 240 (54), 194 (4), 157 (6), 140 (35), 121 (16), 106 (25), 95 (10), 86 (12).

Elemental Analysis for $C_{21}H_{32}N_2O_4$ (376.49): Calcd.: C 66.99; H 8.57; N 7.44.
Found: C 66.79; H 8.83; N 7.48.

5.5.13 Synthesis of (1*R*,2*R*)-cyclopentane-1,2-dicarboxylic acid 1-[(2'-hydroxy-1'-(*S*)-methyl-ethyl)-amide]-2-[(2'-hydroxy-1'-(*S*)-phenyl-ethyl)-amide] (247)



Solid EEDQ (1.19 g, 4.80 mmol, 1.2 eq.) was added at 0 °C to a solution of **246** (0.861 g, 4.00 mmol) and (*S*)-phenylglycinol (0.549 g, 4.00 mmol, 1.0 eq.) in dry THF (40.0 mL) and the mixture was stirred at r.t. for 5 days. The solvent was removed in vacuum and the crude reaction product was purified by column chromatography (pentane:EtOAc, 1:1 + 5% MeOH) delivering the title compound in 82% yield (1.10 g, 3.29 mmol) as a white solid.

Mp: 235 °C.

$[\alpha]^{rt}_D$ = +1.6 (*c* = 0.55, MeOH).

^{1}H-NMR (400 MHz, CD_3OD): δ = 0.93 (d, *J* = 6.9 Hz, 3H), 1.69-1.86 (m, 4H), 1.95-2.07 (m, 2H), 2.77 (q, *J* = 8.8 Hz, 1H), 2.98 (q, *J* = 8.8 Hz, 1H), 3.35 (dd, *J* = 5.8, 11.0 Hz, 1H), 3.40 (dd, *J* = 5.5, 11.0 Hz, 1H), (3.35/3.40 AB part of an ABX-system), 3.65 (dd, *J* = 7.4, 11.3 Hz, 1H), 3.70 (dd, *J* = 5.5, 11.3 Hz, 1H), (3.65/3.70 AB part of an ABX-system), 3.80-3.88 (m, 1H), 4.94 (dd, *J* = 5.5, 7.4 Hz, 1H), 7.19-7.22 (m, 1H), 7.23 (d, *J* = 4.4 Hz, 4H).

^{13}C-NMR (100 MHz, CD_3OD): δ = 15.8, 25.0, 30.6, 31.0, 47.0, 55.7, 64.7, 64.9, 126.5, 126.8, 128.0, 139.9, 175.2, 175.5.

IR (KBr): 3290, 2959, 1643, 1553, 1040 cm^{-1}.

EI-MS: m/z = 335 (M^++1, 2), 303 (M^+-31, 64), 260 (21), 198 (71), 180 (11), 140 (24), 121 (12), 106 (46), 95 (13), 67 (10), 58 (21).

Elemental Analysis for $C_{18}H_{26}N_2O_4 \cdot H_2O$ (334.41+H_2O):

Calcd.: C 64.65; H 7.84; N 8.38.

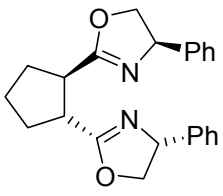
Found: C 64.45; H 8.07; N 8.26.

5.6 Synthesis of C_2- and C_1-symmetric chiral bisoxazolines with cyclopentane as backbone

5.6.1 General procedure for the preparation of various C_2- and C_1-symmetric chiral bisoxazolines with cyclopentane as backbone (GP-7)

Diethylaminosulfur trifluoride (0.67 mL, 5.50 mmol, 2.2 eq.) was added dropwise to a cooled (–78 °C) suspension of the corresponding bis-hydroxyamide (2.50 mmol) in dry CH_2Cl_2 (25.0 mL). After stirring for 3-5 h at the indicated temperature, anhydrous K_2CO_3 (1.04 g, 7.50 mmol, 3.0 eq.) was added and the reaction mixture was allowed to warm to r.t.. A saturated aq. $NaHCO_3$ solution was added and after phase separation the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, filtered and concentrated in vacuum to yield the crude product which was purified by column chromatography.

5.6.2 Synthesis of (1*R*,2*R*)-bis-[4'-(*R*)-phenyl-oxazolin-2'-yl]-cyclopentane (228)



The product was synthesized from **221** (0.991 g, 2.50 mmol) according to GP-7. Purification by column chromatography (pentane:EtOAc, 1:2) yielded 0.818 g (2.27 mmol, 90%) of the title compound as a colorless oil.

$[\alpha]^{rt}_D$ = –20.8 (*c* = 0.65, $CHCl_3$).

^{1}H-NMR (300 MHz, $CDCl_3$): δ = 1.72-1.82 (m, 2H), 1.86-1.98 (m, 2H), 2.06-2.17 (m, 2H), 3.20-3.30 (m, 2H), 4.02 (t, *J* = 8.2 Hz, 2H), 4.54 (dd, *J* = 8.2, 10.1 Hz, 2H), 5.10 (dd, *J* = 7.9, 10.1 Hz, 2H), 7.13-7.26 (m, 10H).

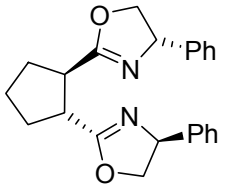
^{13}C-NMR (75 MHz, $CDCl_3$): δ = 25.5, 31.3, 42.6, 69.6, 75.0, 126.7, 127.5, 128.7, 142.7, 170.3.

IR (capillary): 3061, 3029, 2962, 2899, 1660, 1493, 1453, 1360, 1177, 1079 cm^{-1}.

EI-MS: m/z = 360 (M^+, 96), 242 (59), 214 (100), 199 (15), 187 (20), 174 (45), 120 (12), 104 (48), 95 (21), 91 (27), 67 (17).

HRMS for $C_{23}H_{24}N_2O_2$: Calcd.: 360.183780.
Found: 360.183767.

5.6.3 Synthesis of (1*R*,2*R*)-bis-[4'-(*R*)-phenyl-oxazolin-2'-yl]-cyclopentane (229)



The product was synthesized from **222** (0.991 g, 2.50 mmol) according to GP-7. Purification by column chromatography (pentane:EtOAc, 1:2) yielded 0.721 g (2.00 mmol, 80%) of the title compound as a colorless oil.

$[\alpha]^{rt}_D$ = –189.6 (*c* = 3.00, $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.80-1.89 (m, 2H), 1.95-2.04 (m, 2H), 2.15-2.23 (m, 2H), 3.28-3.35 (m, 2H), 4.09 (t, *J* = 8.2 Hz, 2H), 4.63 (dd, *J* = 8.5, 10.2 Hz, 2H), 5.18 (dd, *J* = 8.0, 10.2 Hz, 2H), 7.22-7.33 (m, 10H).

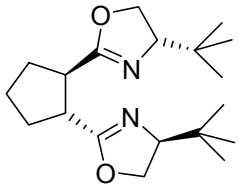
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 25.5, 31.2, 42.6, 69.6, 75.1, 126.6, 127.5, 128.7, 142.5, 170.5.

IR (in $CHCl_3$): 2964, 2900, 1660, 1494, 1453, 1359, 1176, 1026 cm^{-1}.

EI-MS: m/z = 360 (M^+, 96), 242 (48), 214 (100), 199 (16), 187 (24), 174 (55), 120 (54), 104 (51), 95 (21), 91 (26), 67 (17).

HRMS for $C_{23}H_{24}N_2O_2$: Calcd.: 360.183780.
Found: 360.183806.

5.6.4 Synthesis of (1*R*,2*R*)-bis-[4'-(*S*)-*tert*-butyl-oxazolin-2'-yl]-cyclopentane (230)



The product was synthesized from **224** (0.891 g, 2.5 mmol) according to GP-7. Purification by column chromatography (pentane:EtOAc, 1:2) yielded 0.742 g (2.31 mmol, 92% yield) of the title compound as a white solid.

Mp: 53.5-54.5 °C.

$[\alpha]^{rt}_D$ = −186.9 (*c* = 1.08, $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.86 (s, 18 H), 1.72-1.89 (m, 4H), 2.02-2.10 (m, 2H), 3.13 (t, *J* = 5.8 Hz, 2H), 3.79 (dd, *J* = 7.4, 9.9 Hz, 2H), 4.04 (dd, *J* = 7.4, 8.5 Hz, 2H), 4.12 (dd, *J* = 8.5, 9.9 Hz, 2H).

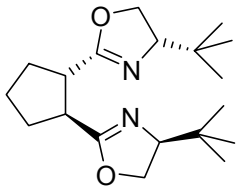
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 25.4, 25.7, 31.3, 33.7, 42.0, 68.5, 75.3, 168.7.

IR (KBr): 2959, 2905, 2869, 1670, 1480, 1359, 1258, 1229, 1019 cm^{-1}.

EI-MS: m/z = 320 (M^+, 14), 305 (6), 263 (100), 205 (6), 194 (15), 163 (24), 136 (21), 95 (2), 67 (3).

Elemental Analysis for $C_{19}H_{32}N_2O_2$ (320.47): Calcd.: C 71.21; H 10.06; N 8.74.
Found: C 70.81; H 9.74; N 8.68.

5.6.5 Synthesis of (1*S*,2*S*)-bis-[4'-(*S*)-*tert*-butyl-oxazolin-2'-yl]-cyclopentane (231)



The product was synthesized from **225** (0.891 g, 2.50 mmol) according to GP-7. Purification by column chromatography (pentane:EtOAc, 1:2) yielded 0.663 g (2.07 mmol, 83%) of the title compound as a white solid.

Mp: 51 °C.

$[\alpha]^{rt}_D$ = +2.5 (*c* = 0.69, $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.87 (s, 18 H), 1.70-1.77 (m, 2H), 1.81-1.89 (m, 2H), 2.00-2.08 (m, 2H), 3.09-3-16 (m, 2H), 3.80 (dd, *J* = 7.4, 10.2 Hz, 2H), 4.03 (dd, *J* = 7.4, 8.5 Hz, 2H), 4.12 (dd, *J* = 8.5, 10.2 Hz, 2H).

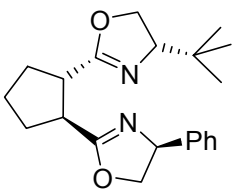
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 25.4, 25.7, 31.2, 33.6, 42.1, 68.5, 75.3, 168.5.

IR (KBr): 2956, 2902, 2873, 1670, 1476, 1360, 1249, 1188 cm^{-1}.

EI-MS: m/z = 320 (M^+, 15), 305 (5), 263 (100), 205 (4), 194 (9), 163 (15), 136 (18).

HRMS for $C_{19}H_{32}N_2O_2$: Calcd.: 320.246378.
Found: 320.246389.

5.6.6 Synthesis of (1*S*,2*S*)-[4'-(*S*)-*tert*-butyl-oxazolin-2'-yl]-[4''-(*S*)-phenyl-oxazolin-2''-yl]-cyclopentane (245)



The product was synthesized from **234** (0.941 g, 2.50 mmol) according to GP-7. Purification by column chromatography (pentane:EtOAc, 1:2) yielded 0.705 g (2.07 mmol, 83% yield) of the title compound as a colorless oil.

$[\alpha]^{rt}_D$ = +9.6 (*c* = 1.56, $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.88 (s, 9H), 1.77-1.98 (m, 4H), 2.04-2.15 (m, 2H), 3.17-3.28 (m, 2H), 3.83 (ddd, *J* = 0.8, 7.7, 10.2 Hz, 1H), 4.06 (dd, *J* = 7.7, 8.8 Hz, 1H), 4.07 (dd, *J* = 8.0, 8.2 Hz, 1H), 4.16 (dd, *J* = 8.8, 10.2 Hz, 1H), 4.59 (dd, *J* = 8.2, 9.9 Hz, 1H), 5.14 (dd, *J* = 8.0, 9.9 Hz, 1H), 7.21-7.28 (m, 3H), 7.30-7.35 (m, 2H).

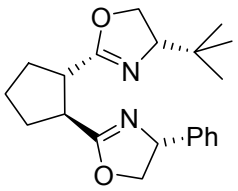
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 25.4, 25.7, 31.1, 31.2, 33.6, 42.1, 42.2, 68.5, 69.4, 74.8, 75.3, 126.4, 127.2, 128.4, 142.4, 168.4, 170.3.

IR (capillary): 2957, 2902, 2872, 1664, 1477, 1454, 1361, 1180, 1025 cm^{-1}.

EI-MS: m/z = 340 (M^+, 39), 325 (4), 283 (100), 242 (11), 214 (29), 163 (55), 136 (34), 120 (13), 103 (7), 95 (8), 67 (8).

HRMS for $C_{21}H_{28}N_2O_2$: Calcd.: 340.215078.
Found: 340.215054.

5.6.7 Synthesis of (1*S*,2*S*)-[4'-(*S*)-*tert*-butyl-oxazolin-2'-yl]-[4''-(*R*)-phenyl-oxazolin-2''-yl]-cyclopentane (246)



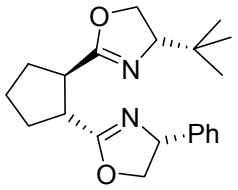
The product was synthesized from **238** (0.941 g, 2.50 mmol) according to GP-7. Purification by column chromatography (pentane:EtOAc, 1:2) yielded 0.692 g (2.03 mmol, 81%) of the title compound as a white solid.

Mp: 61 °C.

$[\alpha]^{rt}_D$ = +110.2 (*c* = 1.00, $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.88 (s, 9H), 1.76-2.04 (m, 4H), 2.05-2.18 (m, 2H), 3.15-3.26 (m, 2H), 3.84 (ddd, *J* = 0.8, 7.4, 10.2 Hz, 1H), 4.05 (dd, *J* = 8.0, 8.5 Hz, 1H), 4.06 (dd, *J* = 7.4, 8.5 Hz, 1H), 4.16 (dd, *J* = 8.5, 10.2 Hz, 1H), 4.59 (dd, *J* = 8.5, 10.2 Hz, 1H), 5.14 (dd, *J* = 8.0, 10.2 Hz, 1H), 7.21-7.27 (m, 3H), 7.30-7.35 (m, 2H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 25.3, 25.9, 31.0, 31.2, 33.8, 42.4, 43.1, 68.8, 69.5, 74.9, 75.6, 126.6, 127.4, 128.6, 142.6, 168.4, 170.5.
IR (KBr): 2952, 2874, 1668, 1476, 1451, 1398, 1352, 1245, 1180, 1026, 1004 cm^{-1}.
EI-MS: m/z = 340 (M^+, 25), 283 (100), 242 (8), 214 (28), 163 (76), 136 (62), 120 (19), 103 (11), 95 (11), 67 (13).
Elemental Analysis for $C_{21}H_{28}N_2O_2$ (340.46): Calcd.: C: 74.08; H: 8.29; N: 8.23.
Found: C: 73.94; H: 7.95; N: 8.23.

5.6.8 Synthesis of (1*R*,2*R*)-[4'-(*S*)-*tert*-butyl-oxazolin-2'-yl]-[4''-(*R*)-phenyl-oxazolin-2''-yl]-cyclopentane (247)



The product was synthesized from **244** (0.941 g, 2.50 mmol) according to GP-7. Purification by column chromatography (pentane:EtOAc, 1:2) yielded 0.712 g (2.09 mmol, 83%) of the title compound as a colorless oil.

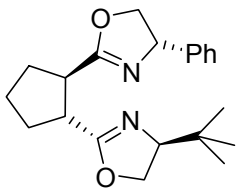
$[\alpha]^{rt}_D$ = –96.9 (*c* = 2.00, $CHCl_3$).
^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.88 (s, 9H), 1.77-2.00 (m, 4H), 2.07-2.18 (m, 2H), 3.16-3.23 (m, 2H), 3.83 (dd, *J* = 7.4, 10.2 Hz, 1H), 4.06 (dd, *J* = 7.4, 8.5 Hz, 1H), 4.07 (dd, *J* = 8.0, 8.2 Hz, 1H), 4.16 (dd, *J* = 8.5, 10.2 Hz, 1H), 4.59 (dd, *J* = 8.2, 10.2 Hz, 1H), 5.14 (dd, *J* = 8.0, 10.2 Hz, 1H), 7.21-7.28 (m, 3H), 7.30-7.35 (m, 2H).
^{13}C-NMR (100 MHz, $CDCl_3$): δ = 25.4, 25.9, 31.1, 31.2, 33.9, 42.6, 42.6, 68.7, 69.6, 75.0, 75.5, 126.6, 127.4, 128.6, 142.6, 168.6, 170.4.

IR (capillary): 2957, 2902, 2872, 1665, 1477, 1361, 1180, 1025 cm^{-1}.

EI-MS: m/z = 340 (M^+, 36), 283 (100), 242 (7), 214 (30), 163 (72), 136 (51), 120 (20), 103 (10), 95 (9), 67 (10).

HRMS for $C_{21}H_{28}N_2O_2$: Calcd.: 340.215078.
Found: 340.215017.

5.6.9 Synthesis of (1*S*,2*S*)-[4'-(*S*)-*tert*-butyl-oxazolin-2'-yl]-[4''-(*S*)-phenyl-oxazolin-2''-yl]-cyclopentane (248)



The product was synthesized from **241** (0.941 g, 2.50 mmol) according to GP-7. Purification by column chromatography (pentane:EtOAc, 1:2) yielded 0.719 g (2.11 mmol, 84% yield) of the title compound as a white solid.

Mp: 36 °C.

$[\alpha]^{rt}_D$ = −197.3 (*c* = 1.02, $CHCl_3$).

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 0.87 (s, 9H), 1.77-1.99 (m, 4H), 2.08-2.18 (m, 2H), 3.16-3.26 (m, 2H), 3.82 (dd, *J* = 7.1, 9.9 Hz, 1H), 4.05-4.09 (m, 1H), 4.07 (dd, *J* = 7.1, 8.5 Hz, 1H), 4.16 (dd, *J* = 8.5, 9.9 Hz, 1H), 4.59 (dd, *J* = 8.2, 10.2 Hz, 1H), 5.15 (dd, *J* = 8.0, 10.2 Hz, 1H), 7.21-7.28 (m, 3H), 7.30-7.34 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 25.5, 25.9, 31.3, 31.4, 33.9, 42.3, 42.6, 68.7, 69.5, 75.0, 75.5, 126.6, 127.4, 128.6, 142.6, 168.7, 170.6.

IR (KBr): 2956, 2904, 2875, 1667, 1360, 1189 cm^{-1}.

EI-MS: m/z = 340 (M^+, 51), 283 (100), 242 (6), 214 (21), 163 (46), 136 (31), 120 (10), 103 (6), 95 (6), 67 (6).

Elemental Analysis for $C_{21}H_{28}N_2O_2$ (340.46): Calcd.: C: 74.08; H: 8.29; N: 8.23.
Found: C: 74.14; H: 8.64; N: 8.08.

5.7 Applications in the catalysis

5.7.1 General procedure for the asymmetric cyclopropanation reaction (GP-7)

A solution of the corresponding ligand (0.015 mmol, 1.05 mol%) in dry CH_2Cl_2 was added *via* syringe to a flask containing $CuOTf{\cdot}0.5C_6H_6$ (3.5 mg, 0.014 mmol, 1 mol%) under argon. After stirring at r.t. for 1 h, the mixture was cooled to 0 °C. Styrene (1.7 mL, 14.00 mmol, 10.0 eq.) was added followed by slow addition of a solution of ethyl diazoacetate (0.16 g, 1.40 mmol in 2.5 mL CH_2Cl_2) over 5 h *via* syringe pump. The mixture was allowed to warm to r.t. and it was stirred for an additional 16 h before quenching with a 10% aq. solution of NH_4Cl (5.0 mL). The solution was diluted with Et_2O (25.0 mL) and washed with water (5.0 mL) and brine (5.0 mL). The organic layer was dried over $MgSO_4$, filtered and the solvent was removed in vacuum to yield the cyclopropanated products as a mixture of *cis* and *trans* isomers. The diastereomeric ratio was determined by ^{1}H NMR analysis of the crude reaction mixture. In order to determine the enantiomeric excesses, the *cis* and *trans* isomers have been separated by column chromatography (2% ethylacetate in pentane). The ee of the *trans* isomer was determined by HPLC analysis, while comparison of optical rotation was used for the *cis* isomer. The absolute configuration of the products was confirmed by the sign of the optical rotation.

ee = 83% [HPLC-analysis: Chiralcel OD-H at r.t., *n*-heptane:2-propanol = 95:5, 0.5 mL/min, 254 nm, t_1 = 9.6 min (major, (1*R*,2*R*)), t_2 = 12.0 min].

^{1}H-NMR (400 MHz, $CDCl_3$): δ = 1.28 (t, *J* = 7.1 Hz, 3H), 1.29-1.33 (m, 1H), 1.60 (ddd, *J* = 4.1, 5.2, 9.1 Hz, 1H), 1.90 (ddd, *J* = 4.1, 5.2, 8.2 Hz, 1H), 2.51 (ddd, *J* = 4.1, 6.6, 9.3 Hz, 1H), 4.17 (q, *J* = 7.1 Hz, 2 H), 7.08-7.11 (m, 2H), 7.17-7.22 (m, 1H), 7.25-7.29 (m, 2 H).

^{13}C-NMR (100 MHz, $CDCl_3$): δ = 14.2, 17.0, 24.1, 26.1, 60.6, 126.0, 126.3, 128.3, 139.9, 173.1.

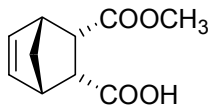
5.7.2 General procedure for the Asymmetric Diels-Alder reaction (GP-8)

A mixture of $Cu(OTf)_2$ or $CuCl_2$ (0.025 mmol, 10 mol%) and the ligand (0.0275 mmol, 11 mol%) in dry CH_2Cl_2 was stirred for 2 h at r.t. under argon. In the case of the counterion screening, silver salts (0.05 mmol) were added to the precursor complex synthesized from $CuCl_2$. Stirring was continued for 30 min and the catalysis was started by adding the dienophile (0.25 mmol), followed by freshly distilled cyclopentadiene. The reaction was monitored by t.l.c. and stopped by filtration through a plug of silica gel using CH_2Cl_2 as solvent. Evaporation of the solvent and purification by column chromatography affords the product as a white solid. The *endo*/*exo* ratio was determined by ^1H NMR analysis of the reaction mixture and confirmed by HPLC analysis.

endo/*exo* = 77:23; **ee**$_{endo}$ = 71% [HPLC-analysis: Chiralcel OD-H at r.t., *n*-heptane:2-propanol = 98:2, 1.0 mL/min, 210 nm, t_1 (*exo*) = 27.7 min, t_2 (*endo*, major) = 32.0 min, t_2 (*endo*, minor) = 34.9 min].

5.8 Synthesis of the salen type ligand

5.8.1 Synthesis of (2*R*,3*S*)-3-*endo*-methoxycarbonyl-bicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylic acid (176)



The product was obtained according to GP-4 from the quinidine opening of anhydride **160** in 97% yield (7.63 g, 38.88 mmol) as a white solid.

Mp: 74 °C (rac), 75-78 °C (en), lit.[277] mp: 74-76 °C (rac).

$[\alpha]^{rt}_D$ = +7.73 (c = 4.0, CCl_4), lit.[277] $[\alpha]^{rt}_D$ = +7.90 (*c* = 4.8, CCl_4).

ee = 98% [GC-analysis of the lactone: Lipodex E, t_1 = 80.7, t_2 = 81.1 (major)].

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.27 (d, *J* = 8.7 Hz, 1H), 1.42 (dt, *J* = 1.7, 8.7 Hz, 1H), 3.07-3.14 (m, 2H), 3.21 (dd, *J* = 3.0, 10.1 Hz, 1H), 3.27 (dd, *J* = 3.0, 10.1 Hz, 1H), 3.52 (s, 3H), 6.14 (dd, *J* = 3.0, 5.7 Hz, 1H), 6.25 (dd, *J* = 3.0, 5.7 Hz, 1H), 10.80 (br s, 1H).

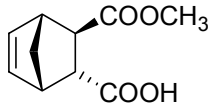
^{13}C NMR (75 MHz, $CDCl_3$): δ = 46.2, 46.7, 48.2, 48.4, 48.9, 51.6, 134.3, 135.7, 172.5, 178.8.

IR (KBr): 3071, 3002, 2949, 2877, 1746, 1709, 1434, 1339, 1259, 1233, 1188, 1049 cm^{-1}.

EI-MS: m/z = 196 (M^+, 2), 178 (7), 165 (M^+–31, 15), 137 (10), 131 (53), 119 (21), 113 (17), 99 (19), 91 (12), 66 (100).

Elemental Analysis for $C_{10}H_{12}O_4$ (196.20): Calcd.: C 61.22; H 6.16.
Found: C 61.43; H 6.16.

5.8.2 Synthesis of (2*R*,3*R*)-3-*exo*-methoxycarbonyl-bicyclo[2.2.1]hept-5-ene-2-*endo*-carboxylic acid (255)



A freshly prepared LDA solution (3.0 eq.) in absolute THF (0.75 mL/mmol LDA) was added dropwise, over 1.5 h, to a stirred solution of the monomethylester (5.89 g, 30.0 mmol) in absolute THF (45.0 mL) at –78 °C under Ar. After the complete addition, the mixture was stirred at this temperature for 4 h, acidified with 4 N aq. HCl and extracted with ethylacetate. The combined organic phases were dried over $MgSO_4$, concentrated, and the residue was purified by column chromatography (pentane:Et_2O, 1:1 + 1% acetic acid) to yield 4.77 g (25.00 mmol, 83% yield) of the title compound as a white solid.

Mp: 95.5 °C (rac), 73 °C (en), lit.[278] mp: 78-79 °C (en).

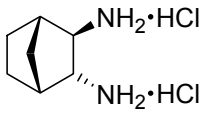
$[\alpha]^{rt}_D$ = −152.40 (c = 1.54 $CHCl_3$), lit.[278] $[\alpha]^{rt}_D$ = −184.20 (c = 1.52 $CHCl_3$).

^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.41 (dq, *J* = 1.7, 8.9 Hz, 1H), 1.56 (dt, *J* = 1.5, 8.9 Hz, 1H), 2.59 (dd, *J* = 1.5,4.7 Hz, 1H), 3.06-3.08 (m, 1H), 3.21-3.24 (m, 1H), 3.36 (dd, *J* = 4.0, 4.5 Hz, 1H), 3.65 (s, 3H), 6.07 (dd, *J* = 2.7, 5.7 Hz, 1H), 6.22 (dd, *J* = 3.2, 5.5 Hz, 1H), 10.20 (br s, 1H).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 45.8, 47.2, 47.7, 47.8, 48.2, 52.4, 135.4, 140.0, 175.0, 179.6.

Elemental Analysis for $C_{10}H_{12}O_4$ (196.20): Calcd.: C 61.22; H 6.16.
Found: C 61.43; H 6.16.

5.8.3 Synthesis of (2*R*,3*R*)-bicyclo[2.2.1]heptane-2-*endo*-3-*exo*-diamine dihydrochloric salt (3·2HCl) (254)



Ethyl chloroformate (3.82 mL, 40.00 mmol, 4.0 eq) was added to a mixture of (2*R*,3*R*)-bicyclo[2.2.1]heptane-2-*endo*-3-*exo*-dicarboxylic acid (1.84 g, 10.00 mmol) and Et_3N (8.36 mL, 60.00 mmol, 6.0 eq.) in THF (16.0 mL) at –20 °C and the reaction mixture was stirred at this temperature for 1 h. A solution of NaN_3 (3.90 g, 60.00 mmol, 6.0 eq.) in H_2O (24.0 mL) was added at –10 °C. The temperature was gradually increased to r.t. and stirring continued for 2 h. The mixture was diluted with water, extracted with EtOAc and the organic phase was washed with $NaHCO_3$, dried over $MgSO_4$, filtered and concentrated to provide the coresponding acyl azide **6**, which was dissolved in benzene (16.0 mL) and heated under reflux for 2 h. To the cooled isocyanate solution conc. aq. HCl (30.0 mL) was added and the resulting mixture was refluxed for 4 h. The reaction mixture was extracted with Et_2O and the aqueous layer was concentrated to give a solid which was washed with THF and dried in high vacuum to give 1.4 g (7.05 mmol, 70% yield) of the title compound as a colorless solid.

Mp: >250 °C (rac, en), lit.[257] mp: >350 °C (rac).

$[\alpha]^{rt}_D$ = –9.3 (c = 1.52, MeOH), $[\alpha]^{rt}_D$ = –16.4 (c = 1.18, H_2O), lit.[254] for *ent*-**3**·2HCl: $[\alpha]^{rt}_D$ = +26.0 (c = 2.0, MeOH).

^{1}H NMR (400 MHz, DMSO-d^6): δ = 1.22 (d, *J* = 10.2 Hz, 1H), 1.30-1.39 (m, 2H), 1.49-1.59 (m, 2H), 1.98 (d, *J* = 10.2 Hz, 1H), 2.3 (s, 1H), 2.95 (s, 1H), 3.30 (s, 1H), 3.46 (s, 1H), 8.54 (s, 3H), 8.59 (s, 3H).

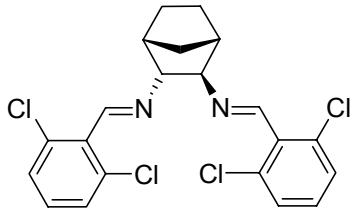
^{13}C NMR (100 MHz, DMSO-d^6): δ = 21.0, 27.5, 35.3, 39.8, 40.9, 57.2, 58.0.

IR (KBr): 2970, 2614, 1604, 1565, 1496, 1120, 1061 cm^{-1}.

EI-MS: m/z = 126 (44), 108 (16), 97 (20), 92 (18), 85 (25), 70 (43), 56 (100).

Elemental Analysis for $C_7H_{16}Cl_2N_2$ (199.12): Calcd.: C 42.22; H 8.10; N 14.07.
Found: C 42.22; H 8.19; N 14.00.

5.8.4 Synthesis of (2*R*,3*R*)-*N,N'*-bis-(2,6-dichloro-benzylidene)-bicyclo[2.2.1] heptane-2-*endo*-3-*exo*-diamine (257)



To a solution of **3**·2HCl (398.24 mg, 2.00 mmol) and 2,6-dichlorobenzaldehyde (700 mg, 4.00 mmol, 2.0 eq.) in MeOH was added Et_3N (4.17 mL, 30.00 mmol, 15.0 eq), and the mixture was stirred for 16 h at r.t. The solvent was removed in vacuum to give a solid which was dissolved in CH_2Cl_2, washed with water, dried over $MgSO_4$ and concentrated to provide 0.81 g (1.84 mmol, 92% yield) of the title compound as a white solid.

Mp: 85.0 °C (en).

$[\alpha]^{rt}_D$ = –128.00 (c = 1.00, $CHCl_3$).

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.48-1.60 (m, 3H), 1.70-1.79 (m, 1H), 2.16-2.23 (m, 2H), 2.40 (d, *J* = 4.1 Hz, 1H), 2.51 (br s, 1H), 3.41 (t, *J* = 2.2 Hz, 1H), 3.75 (br s, 1H), 7.20 (dd, *J* = 7.4, 8.5 Hz, 2H), 7.31 (d, *J* = 3.1 Hz, 2H), 7.33 (d, *J* = 3.0 Hz, 2H), 8.32 (s, 1H), 8.48 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.3, 28.0, 36.8, 44.3, 45.2, 80.8, 81.6, 128.7, 128.8, 130.3, 130.4, 133.6, 133.8, 134.8, 134.8, 155.3, 156.9.

IR (KBr): 2954, 2870, 1642, 1579, 1557, 1429, 1375, 1189, 1094, 781 cm^{-1}.

EI-MS: m/z = 267 (100), 239 (40), 174 (39), 156 (24), 123 (24), 66 (22).

Elemental Analysis for $C_{21}H_{18}Cl_4N_2$ (440.19): Calcd.: C 57.30; H 4.12; N 6.36.
Found: C 57.26; H 3.91; N 6.35.

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7 Abbreviations

$[\alpha]^{rt}_{D}$	specific rotation
Å	angstrom(s)
Ac	acetyl
aq.	aqueous
Ar	aryl
atm	atmosphere(s)
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Box	bisoxazoline
br	broad (spectral)
Bu	butyl
i-Bu	iso-butyl
t-Bu	*tert*-butyl
c	concentration
°C	degrees Celsius
calcd	calculated
cat.	catalyst
Cbz	benzyloxycarbonyl
cm^{-1}	wavenumber(s)
δ	chemical shift in parts per million downfield from tetramethylsilane
d	day(s)
d	doublet (spectral)
DABCO	1,4-diazabicyclo[2.2.2]octane
dd	doublet of doublets (spectral)
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
dr	diastereomeric ratio
de	diastereomeric excess
ee	enantiomeric excess
EI	electronic impact (in mass spectrometry)
eq.	equivalent(s)
Et	ethyl

FAB	fast atom bombardament (in mass spectrometry)
g	gram
GC	gas chromatography
h	hour(s)
HPLC	high-performance liquid chromatography
HRMS	high-resolution mass spectrometry
Hz	hertz
IR	infrared
J	coupling constant in NMR spectrometry
L	ligand
LDA	lithium diisopropylamide
LUMO	lowest unoccupied molecular orbital
m	multiplet (spectral)
M	molar (moles per liter)
M^+	parent molecular ion (in mass spectrometry)
Me	methyl
MHz	megahertz
mL	milliliter(s)
Mp	melting point
MS	mass spectrometry
m/z	mass-to-charge ratio (in mass spectrometry)
NMR	nuclear magnetic resonance
Nu	nucleophile
PG	protecting group
Ph	phenyl
ppm	part(s) per million
i-Pr	isopropyl
q	quartet (spectral)
rac	racemic
r.t.	room temperature
s	singlet (spectral)
t	triplet (spectral)
TADDOL	α, α, α', α'-tetraaryl-2,2-dimethyl-1,3-dioxolan-4,5-dimethanol
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
t.l.c.	thin-layer chromatography

TMS	trimethylsilyl
TMS	tetramethylsilane
t_R	retention time
Ts	p-toluenesulfonyl (tosyl)
TS	transition state

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