α-Amino Acid Derivatives and α-Fluoro Ketones by Enantioselective Decarboxylation

Dissertation

at the

Fakultät für Chemie und Pharmazie

der Universität Regensburg

presented by

Markus A. Baur

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This work was instructed by Prof. Dr. H. Brunner

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Board of examiners: Prof. Dr. H. Brunner

Prof. Dr. F. Hénin

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The work at hand was done in the time interval from January 2001 until June 2003 in the group of Prof. Dr. H. Brunner, Institut für Anorganische Chemie der Universität Regensburg and in the time interval from Dezember 2001 until April 2002 in the group of Prof. Dr. F. Hénin, Unité Mixte de Recherche “Réactions Sélectives et Applications”, CNRS – Université de Reims Champagne-Ardenne.

I want to thank my highly appreciated teacher

Herrn Prof. Dr. H. Brunner

for his high interest in the progress of this work and the excellent working conditions.

For my parents

1 Introduction

1.1 Chirality[1,2]

The phenomenon of chirality is easy to see for everyone of us just by looking at our hands. Left and right hand behave like image and mirror image (Figure 1), but they cannot be superimposed on each other. In 1884 LORD KELVIN introduced the term chirality for this characteristic feature. He deduced it from the Greek word "χειρ" = cheir, which means nothing else as hand. However, it was PASTEUR who was the first to discover chirality in chemistry. In his famous experiment in 1848, he observed two different forms of hemihedral crystals when crystallizing an aqueous solution of sodium ammonium tartrate. By manual resolution just with a hand lens and a pair of tweezers, he separated two different forms of crystals which showed opposite optical rotations in solution.

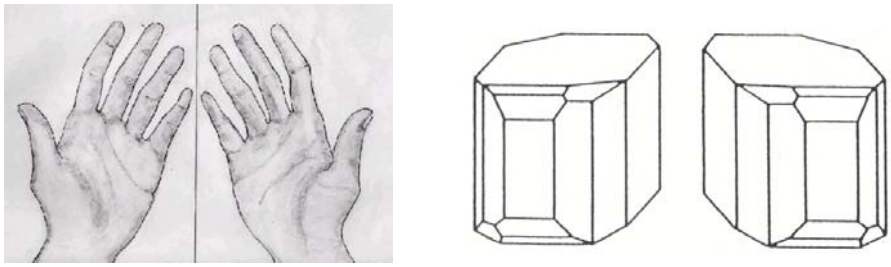


Figure 1: *Chirality of hands[3] and $NaNH_4$ tartrate crystals[2]*

But PASTEUR could not explain what made the difference of the molecular structure of these two kinds of crystals. In 1874, 26 years later, VAN´T HOFF and LE BEL found an explanation for the phenomenon of chirality, reduced to the structural configuration of chemical molecules. Independent from each other, they proposed that the four valencies of a carbon atom are directed towards the corners of a regular tetrahedron. With four different substituents, just two different tetrahedra can be obtained (Figure 2).

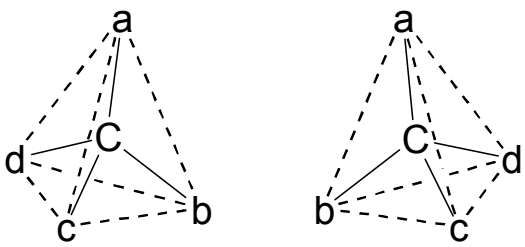


Figure 2: *Asymmetrically substituted carbon atoms enantiomeric to each other*

The two tetrahedra are chiral. They contain no element of symmetry. They are enantiomers. Chirality concerns all life on earth. Many natural compounds only exist as single enantiomers, for example L-amino acids and D-sugars. This phenomenon is called biological homochirality. To date, there are many theories how this homochirality may have developed[2,4,5]. Chiral induction by polarized light or crystallization was proposed for the genesis of biological homochirality on earth. Until today, there is no final theory for this phenomenon.

1.2 Chiral switch[6,7]

The consequences of biological homochirality are extensive. As the receptors of our body are also chiral, the different enantiomers of pharmaceuticals have a different effect on us. The enantiomer with the desired pharmaceutical effect is called eutomer, the one with no or undesired effects is called distomer. In the case of Naproxen®, an anti-inflammatory agent, the (*S*)-enantiomer is 28 times more active than the (*R*)-enantiomer[8] (Figure 3). Therefore, the (*R*)-enantiomer can be seen as isomeric ballast which has to metabolized by the body. Another interesting example is the agent Propanolol®.

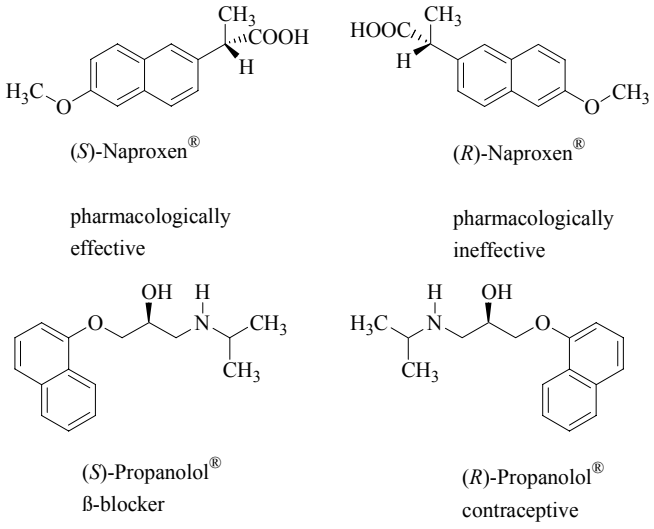
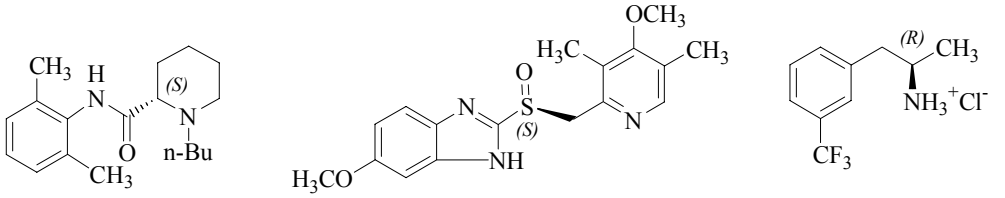


Figure 3: *Different pharmaceutical properties of enantiomers*

While the (*R*)-enantiomer is a ß-blocker and taken in case of hypertension, the (*S*)-form has a completely different effect – it is a contraceptive. These two examples show the pressure towards enantiopure drugs. In 1992 the American Food and Drug

Administration (FDA) complicated the approval of racemic drugs. Other countries followed. Therefore, pharmaceutical companies are urged to develop enantiopure drugs. The development of single enantiomer drugs in place of the previous racemic mixture is called “chiral switch”. Enantiopure pharmaceuticals are also desirable for the producers due to economic aspects. If a drug was patented as a racemate, it is possible to get a new patent for the single enantiomer. Some companies specialized on that niche, for example Sepracor.

The local anaesthetic Bupivacaine®, which was sold as a racemate, made headlines in 1979. Cases of sudden cardiovascular collapse with difficult resuscitation or death were reported. It turned out that the (*S*)-isomer was significantly less cardiotoxic than the antipode and the racemate. Therefore, Bupivacaine® was “switched” to Levobupivacaine® (Figure 4). An example for a current, successful chiral switch is the synthesis of Perprazole®, the (*S*)-form of Omeprazole®. It is a medicament for the treatment of reflux oesophagitis. The single enantiomer shows increased activitity.



Levobupivacaine® Perprazole® Dexfenfluramine®

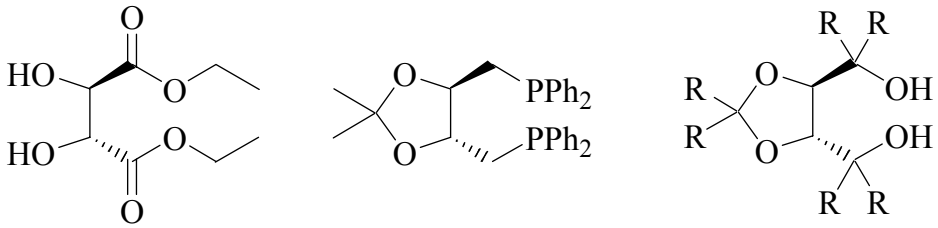
Figure 4: *Three examples for chiral switches*

However, even with enantiopure drugs failures on the pharmaceutical market may happen. One rare example is the luckless introduction of the appetite suppressor Dexfenfluramine® in the market, the D-isomer of the formerly racemic drug Fenfluramine®. First the enantiopure agent showed increased potency and tolerance. Indeed, when in the market, the enantiopure drug caused stronger side effects than the racemic mixture. Due to a perceived risk of pulmonary hypertension, it was withdrawn from the market in 1997.

1.3 Enantioselective catalysis[9,10]

There are different possibilities to obtain enantiopure substances. Separation methods like optical resolution or chromatography imply a waste of substrate and solvents. Furthermore, they are quite work-intensive. It is more efficient to start the synthesis with enantiopure substrates from the "chiral pool", e.g. amino acids or sugars, or to access from the so called "new pool", i. e. commercially available, unnatural chiral substances. But in these cases the synthesis is restricted in terms of suitable and available chiral substrates. Asymmetric synthesis is much more manifold. There are different possibilities for asymmetric synthesis: with enzymes, with chiral auxiliaries or with catalysts. Enzymes are powerful biocatalysts, but sensitive to certain chemicals and restricted to certain substances and reaction classes. Chiral auxiliaries have the disadvantage that they are needed in stoichiometric amounts.

Asymmetric catalysis has some advantages compared to the methods mentioned above. Using a substoichiometric amount of a chiral catalyst, in the best case only the desired enantiomer is obtained and the catalyst can be recycled. Interestingly, many powerful catalysts in modern asymmetric catalysis are derived from the chiral pool. Let us return to PASTEUR´s tartaric acid − with only a slight derivatisation to the ethyl ester, it turned out to be a highly enantioselective cocatalyst in the SHARPLESS epoxydation[11] (Figure 5). The bidentate phosphane ligand DIOP of KAGAN was a breakthrough in the development of hydrogenation of olefins in 1971[12].



DIOP TADDOLs

SHARPLESS *KAGAN* *SEEBACH*

Figure 5: *Successful catalysts derived from tartaric acid*

The TADDOL type ligands from SEEBACH are powerful catalysts for many different reactions, e.g. DIELS-ALDER reactions, [2+2] cycloadditions and addition of Et_2Zn or

Me_3SiCN to aldehydes[13]. These three examples of catalysts show that the derivatisation of a quite simple basic structure from the chiral pool may lead to successful enantioselective catalysts in different chemical reactions.

An asymmetric catalysis which is known for a long time but which gained interest no more than in the last two decades is the enantioselective decarboxylation. In this catalysis, alkaloids from the chiral pool were applied as catalysts and derivatives of them helped to increase the enantiomeric excess. The evolution of this catalysis is described in the next chapter.

2 General Part

2.1 Enantioselective decarboxylation

The first enantioselective decarboxylation reaction was carried out by MARCKWALD in 1904[14,15]. He heated the brucine salt of ethylmethylmalonic acid and obtained 2-methylbutyric acid with 10% ee (Figure 6).

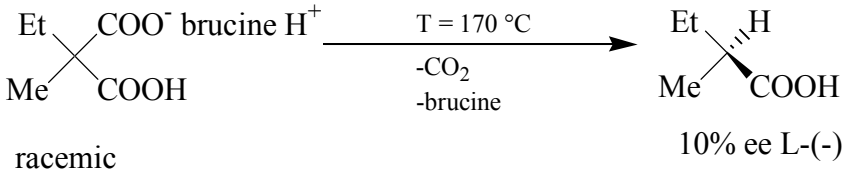


***Figure 6**: First enantioselective decarboxylation by MARCKWALD (1904)*

In the following decades, only few publications followed, all with disappointing results[16,17]. 1986 TOUSSAINT revitalized interest in enantioselective decarboxylation reactions, using copper(I) salts and cinchona alkaloids as catalysts (Figure 7)[18,19]. With 2-alkyl-2-phenylmalonic acid derivatives as substrate he achieved up to 31% ee. He postulated a catalytic cycle based on Cu(I). While the isolation of new Cu(I) malonato

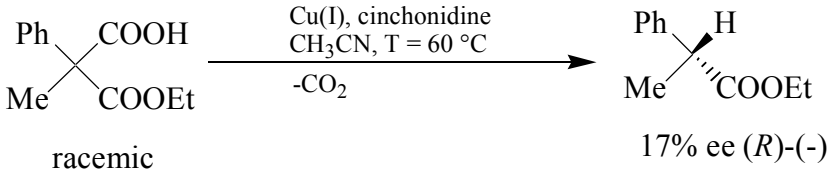


***Figure 7:** Enantioselective decarboxylation using Cu(I) salts, TOUSSAINT*

complexes first confirmed the role of the metal as catalyst in the decarboxylation of malonic acids[20], the importance of copper was questioned in following publications[21,22,23]. It turned out that the reaction was not Cu(I) catalyzed but base catalyzed[22]. Hence, decarboxylations with CuCl were considerably slower than with the much more basic Cu_2O. Therefore, Cu(I) is not necessary as catalyst, the organic nitrogen base on its own is sufficient. Using only 10 mol% of cinchonine as chiral base and no copper(I) salt, the enantiomeric excess in the decarboxylation of ethyl 2-methyl-2-phenylmalonate was increased to 35% ee (compare to Figure 7). Also using only

commercial cinchona alkaloids as catalysts, KIM got optically active β-hydroxyisobutyric acid by enantioselective decarboxylation, but only with 18% ee[24]. Screening different modified cinchona alkaloid derivates as catalysts, SCHMIDT achieved clearly improved chiral induction. With substoichiometric amounts of those modified bases as catalyst, he obtained the Naproxen® derivative 2-(6-methoxynaphtalene-2-yl)propionitrile with up to 72% ee (Figure 8)[25,26]. While natural cinchona alkaloids only induced up to 34% ee, it appeared that benzamide derivatives of 9-amino(9-deoxy)epichinchonine were the most successful catalytically active bases in this system.

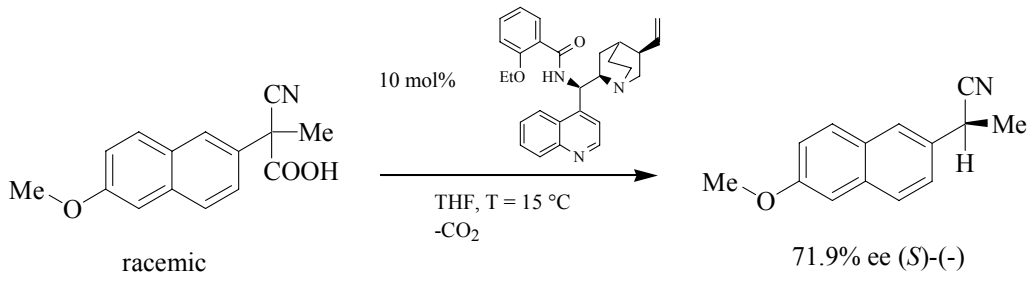


Figure 8: *Enantioselective decarboxylation leading to a Naproxen® derivative*

Parallel to these studies, HÉNIN and MUZART prepared optically active cyclic[27,28,29] ketones *via* palladium-induced cascade reactions, including the enantioselective decarboxylation step. They used benzyl ß-oxo esters as starting material, the ultimate decarboxylation reaction took place after the deprotection of the ß-oxo ester by hydrogenolysis.

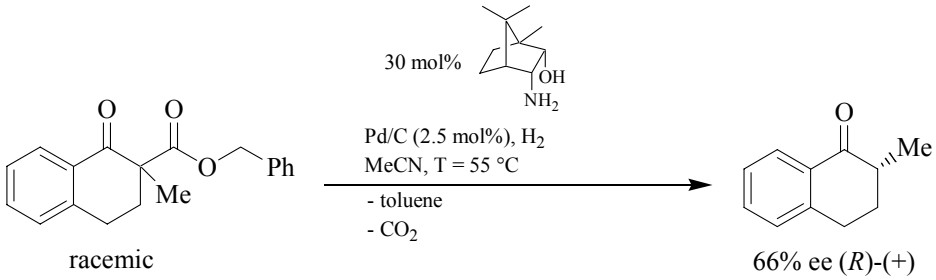


Figure 9: *The Pd-induced cascade reaction arriving at 2-methyl-1-tetralone*

In their cyclic systems, simple ß-aminoalcohols like ephedrine gave better results than cinchona alkaloids. Aminoborneol turned out to be the best catalyst for the 2-methyl-1-tetralone system (Figure 9). With indanone derivatives as substrate even 99.5% ee was achieved.

On the other hand, when they used linear[30,31] starting materials to their cascade reaction, the situation changed. Unmodified cinchona alkaloids afforded promising enantiomeric excess up to 71% ee (Figure 10), while the ß-aminoalcohols which were effective for the cyclic system only gave low inductions up to 16% ee.

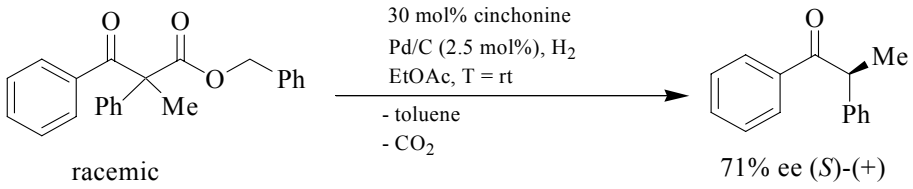


Figure 10: *Applying the Pd-induced cascade reaction to linear substrates*

In my diploma thesis, I applied the enantioselective decarboxylation in order to obtain α-amino acid derivatives[32]. Employing ethyl 2-*N*-acetylamino-2-methylmalonic acid as substrate, 19% ee were obtained with the *ortho*-ethoxy-substituted *N*-(9-deoxyepicinchonine-9-yl)benzamide catalyst from the Naproxen® system (Figure 11). Commercial cinchona alkaloids were inferior.

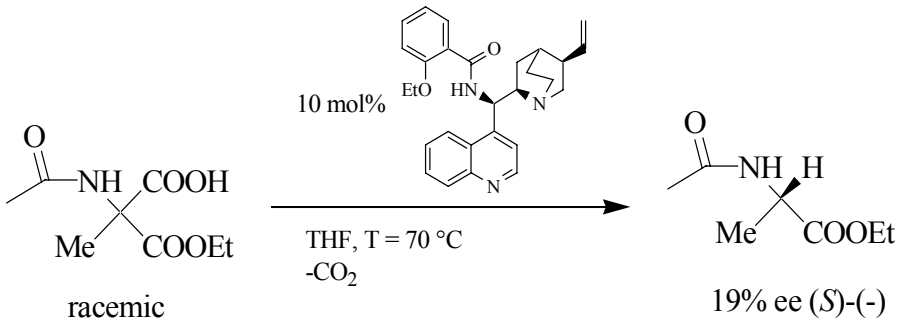


Figure 11: *Arriving at α-amino acid derivative ethyl N-acetylalaninate*

In a recent publication, the group of LASNE reported on a similar system using a cyclic substrate (Figure 12)[33]. In this system, again a derivatised cinchona alkaloid gave the best results.

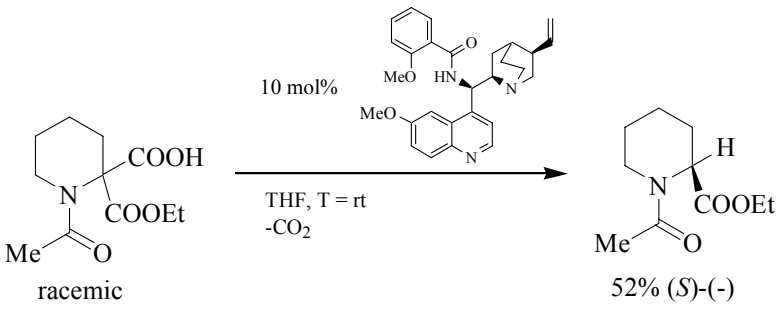


Figure 12: *Arriving at α-amino acid derivative N-acetyl pipecolic acid ethyl ester*

Interestingly, in some cases a "simple" ß-aminoalcohol or an unmodified cinchona alkaloid may also lead to promising enantiomeric excess. Therefore, the origin of the enantiomeric excess in this type of catalysis and the role of the base will be discussed next.

2.2 Protonation of enolic species

How can the optical induction in enantioselective decarboxylation be explained? If a malonic acid derivative or ß-oxo acid is heated, CO_2 separates[34] (Figure 13). This happens *via* a six-membered ring transition state. The generated enol tautomerises and a racemic product is found.

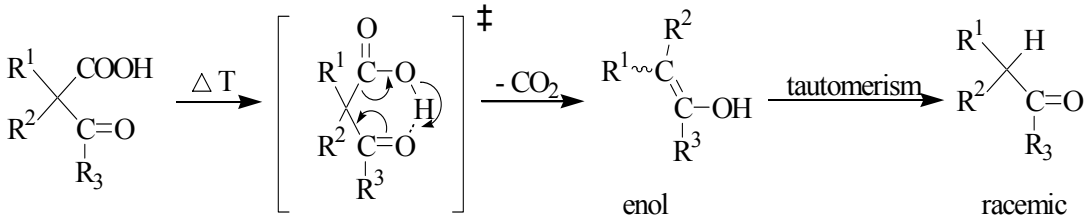


Figure 13: *Thermal decarboxylation of a ß-oxo acid*

In the presence of a chiral base, e.g. cinchona alkaloids or ß-aminoalcohols, after abstraction of the acid proton by the base and decarboxylation, a mesomerically stabilized carbanion originates (Figure 14). The stability of this intermediate depends on the residues R^1, R^2 and R^3. Substituents with –I and –M effects stabilize the negative charge and facilitate the decarboxylation step.

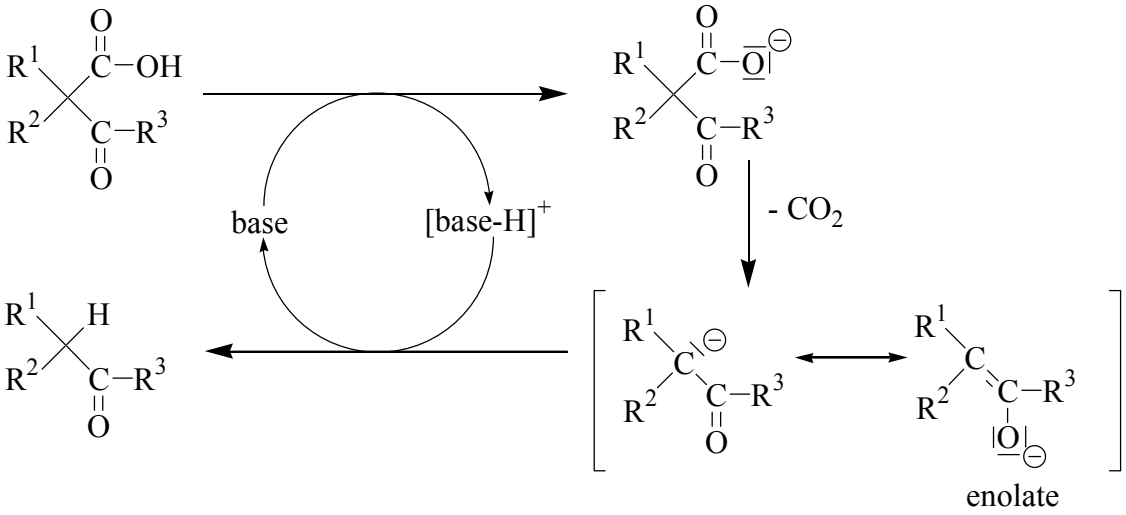


Figure 14: *Mechanism of the base catalysed decarboxylation*

Besides the electronical properties of the substituents, their sterical demand also has to be taken into account. The planar enolate is a prochiral intermediate. With a chiral, protonated base $[B\text{-}H]^+$, the *si* and *re* face protonation should take place at different rates. Therefore, the enantiomers should be obtained in different quantities (Figure 15). After this reprotonation step, the chiral base B is available for another catalytic cycle.

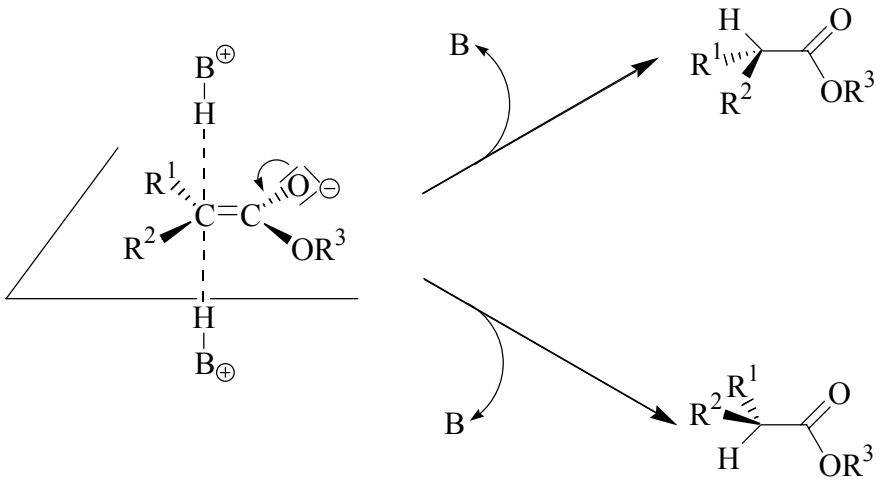


Figure 15: *Enantioselective protonation of the enolate*

Pioneering work in the enantioselective protonation of enolates was done by DUHAMEL[35]. His first "deracemication" of α-amino acid derivatives using Li-salts of secondary amines as base and a tartaric acid derivative as proton source achieved 70% ee. The enantioselective protonation of enolates gained interest and the research on it

increased strongly[36,37,38]. Nevertheless, it is a complex reaction. The proton exchange reactions between the electronegative atoms are very fast, diffusion controlled reactions. Therefore, it is hard to distinguish between the different possible reactants and intermediates. They can transform rapidly into each other. Furthermore, solvation, aggregation and complexation effects affect the kinetically controlled reaction.

There are different possible routes for the formation of the product. The protonation of the enolate at the oxygen results in an enol. This enol could act as an undesired proton source for the C-protonation of the enolate. Depending on the reaction conditions, a partial thermal decarboxylation as described above is also possible. Furthermore, the enol can tautomerise enantioselectively in the prescense of a ß-aminoalcohol (Figure 16). The protonation of the enol was proposed in the following way[39]: The hydrogen

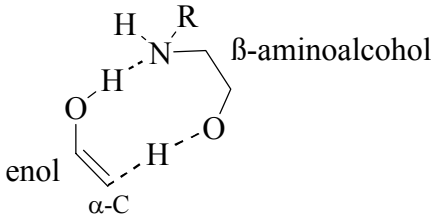


Figure 16: *Enantioselective Tautomerisation (residues R_{1-3} left out)*

bonding between the enol proton and the N-atom increases the electron density at α-C and leads to a more or less concerted proton transfer *via* a cyclic, nine-membered ring transition state.

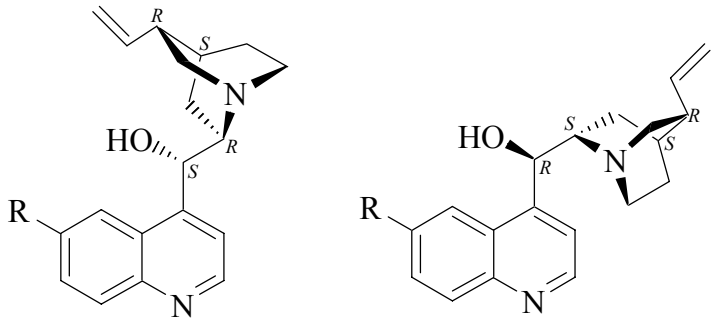
Besides, there is a difference between the catalytic decarboxylation systems starting with a free acid as substrate and those starting from a benzyl protected one. In the case of an unprotected substrate, a catalytic amount (10 mol%) of the chiral base is used. In the protected system, also a substoichiometric amount (30 mol%) of base is applied. But in this case, the real substrate, namely the deprotected acid has to be formed first by the Pd-induced deprotection step. Therefore, there is an excess of base in the reaction mixture. Indeed, the deprotection step bears another possibility which leads to racemisation – the reductive elimination of a Pd-enolate. On the other hand, the Pd-induced cascade reaction method allows to use starting materials which are not stable as free acid.

The structure of the substrate also has to be taken into account. With linear substrates, E/Z isomerism of the enol(ate) has to be considered, while the geometry of cyclic enol(ates) is fixed. But obviously the cyclic substrates are not superior to the linear ones, they just may prefer another catalyst. Concerning the different substituents of the enol(ate), R_3 seems to have only a minor effect on the enantiomeric excess, while R_1 and R_2 do influence the results[30].

As discussed in the previous chapter, alkaloids with a ß-aminoalcohol moiety turned out to be suitable catalysts for the decarboxylation/reprotonation step. In most cases, already unmodified, commercial cinchona alkaloids gave promising results. Moreover, derivatives of them improved the results. Therefore, the class of cinchona alkaloids should be considered more closely.

2.3 Cinchona alkaloids as catalysts

Cinchona alkaloids are natural products, extracted from the dried bark of the cinchona tree (*Cinchona officinalis*)[40]. The mainly isolated products are cinchonine, cinchonidine, quinine and quinidine (Figure 17).



R = H: cinchonine R = H: cinchonidine
R = OMe: quinidine R = OMe: quinine

Figure 17: *Commercially available cinchona alkaloids*

Their structure is based on a quinoline ring which is linked over a hydroxymethylene bridge with a vinylated quinuclidine system. Although cinchonine/cinchonidine and quinidine/quinine are diastereomers, due to the fixed geometry of the quinuclidine residue, they mostly behave like enantiomers.

Further derivatives which are found in the bark are the epibases with reversed configuration for the hydroxy group and the dihydro derivatives with an ethyl residue instead of a vinyl residue attached to the quinuclidine system. The dihydro derivatives are difficult to separate from the vinyl bases. Therefore, commercial cinchona alkaloids contain 5 to 10 percent of the dihydro derivatives.

The numbering of the framework was recommended by RABE, who did pioneering work in the structure determination of this substance class[41]. From their structure, the cinchona alkaloids can be considered as ß-aminoalcohols, concerning their hydroxy function and the nitrogen of the quinuclidine system.

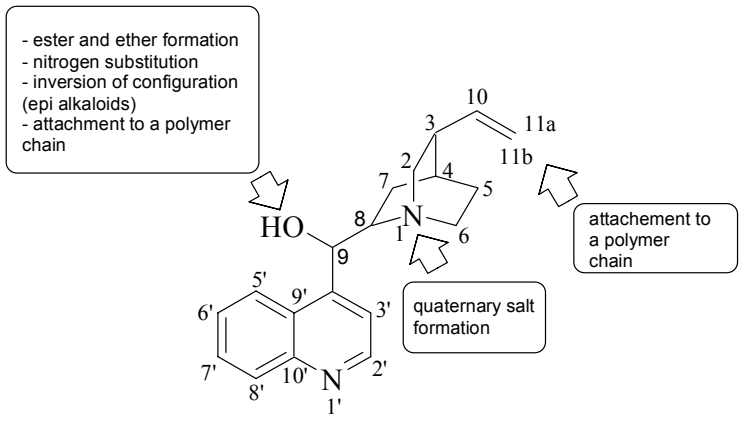


Figure 18: *Derivatisation sites for different catalytic purposes*

With their quinuclidine nitrogen, the vinyl system and the hydroxy group, they have derivatisation sites for different purposes (Figure 18). Cinchona alkaloids and their derivatives are versatile catalysts in modern asymmetric catalysis[42]. Quaternary salts are used for asymmetric phase transfer reactions, for example for α-alkylations of carbonyl compounds[43], Michael additions[44] and epoxidation of enones[45,46]. All three derivatisation sites (quinuclidine N rather rarely) can also be used to attach the molecule to a solid support which enables heterogeneous catalysis. The most common type is the one with the polymer attached to the vinyl group. This heterogeneous catalyst type worked well e.g. for the SHARPLESS asymmetric dihydroxylation (AD) [47]. The hydroxy function at the C9 position allows manifold derivatisations. Ether derivatives for example turned out to be very efficient catalysts in the SHARPLESS asymmetric dihydroxylation (AD)[48] and asymmetric aminohydroxylation (AA) [49].

The replacement of the hydroxy group by an amino group under inversion of configuration afforded 9-amino(9-deoxy)epicinchona alkaloid derivatives which enable the formation of amide, imine and amine derivatives[50,51]. These modified epicinchona alkaloids were applied to different asymmetric catalysis systems: in the addition of diethylzinc to benzaldehyde they gave promising results with almost 80% ee. In asymmetric dihydroxylation of styrene, the hydrogenation of methylpyruvate and the hydrosilylation of acetophenone they were less successful[51]. It appeared that the benzamide derivatives of 9-amino(9-deoxy)epicinchona alkaloids were appropriate catalysts for the enantioselective decarboxylation[25,26].

In the case of enantioselective decarboxylation, the catalyst acts as a base, inducing chirality in the protonation step of the enolic species. With a basicity 10^3 times higher compared to that of the quinoline nitrogen, it is the quinuclidine nitrogen which will take the protonation part. This was confirmed by SCHMIDT, as the benzamide derivative of 9-amino(9-deoxy)epicinchonine with the N-oxide protected quinoline nitrogen gave similar inductions like the unprotected one[25]. With their rigid quinuclidine framework, they are sterical demanding bases in contrast to “simple” ß-aminoalcohols. Furthermore, the different possible conformations due to rotation around the C8-C9 and C4′-C9 bond have to be considered. Conformation analysis was performed and it turned out that the protonated benzamide derivatives prefer an open conformation in solution as well as in the solid state, which means that the quinuclidine nitrogen points away from the quinuclidine ring[52]. Based upon that knowledge, a computational study was published to explain the enantiodiscriminating step in the Naproxen® system[53]. However, this semiempirical calculation led to wrong conclusions (see chapter 4.2.2.4).

Due to the complexity of the protonation of the enol(ate) intermediate, the optimum catalytically active base cannot be “predicted” by rational design. Obviously, the different catalytic systems known to literature need different chiral inductors for improved enantiomeric excess. Therefore, empirical testing of several derivatives for each new catalytic system is necessary.

3 Synthesis

3.1 Goals of this study

In the work at hand, the application of the enantioselective decarboxylation in order to arrive at enantioenriched α-amino acid derivatives, was extended (Figure 19). New substrates were employed and further cinchona alkaloid derivatives were tested as catalytically active bases.

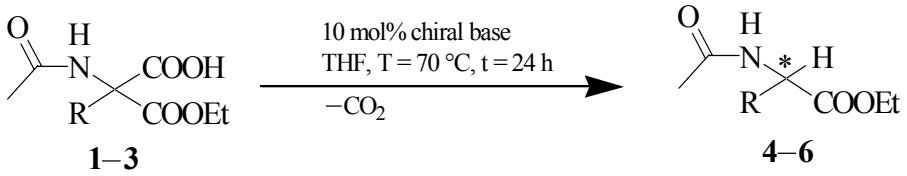


Figure 19: *Enantioselective decarboxylation leading to α-amino acid derivatives*

Furthermore, within the scope of a Marie Curie fellowship at the university of Reims, the Pd induced cascade reaction developed in the group of HÉNIN and MUZART was employed in order to obtain enantioenriched α-fluoro ketones (Figure 20).

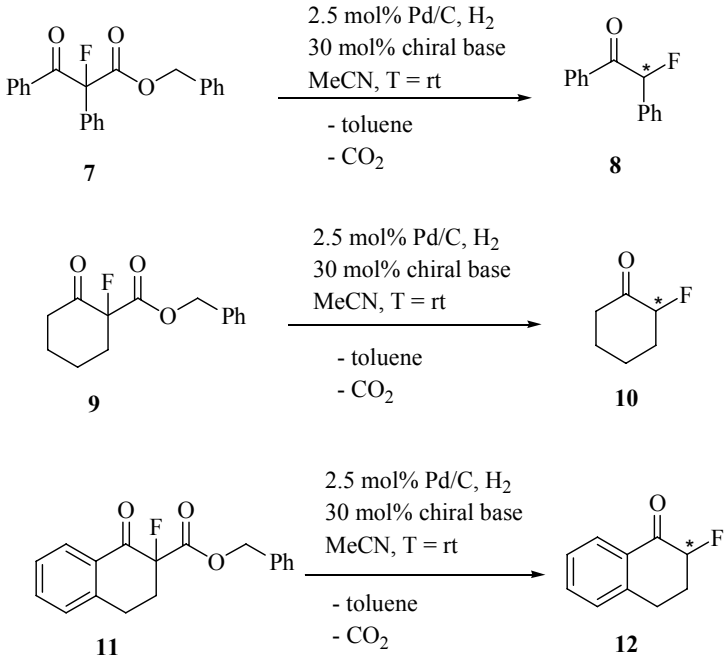


Figure 20: *Enantioselective decarboxylation arriving at α-fluoro ketones*

3.2 Synthesis of substrates for the enantioselective decarboxylation

As most of the synthesised compounds are known to literature or were made analogous to it, this chapter will only give a short overview on the different reactions. The precise description is presented in the experimental part (chapter 5).

3.2.1 Synthesis of 2-*N*-acetylamino-2-alkylmalonic acid monoethyl esters

The substrates for the catalysis leading to α-amino acid derivatives, 2-*N*-acetylamino-2-alkylmalonic acid monoethyl esters, were prepared in two steps, starting from precursor **13** (Figure 21). Diethyl 2-*N*-acetylaminomalonate **13** is also important in industrial amino acid synthesis[54].

In the first step, malonate derivative **13** was alkylated using NaOEt as a base and then refluxed with the appropriate alkyl halide (Figure 21). Synthesis and work-up of **14**[55], **15**[56], **16**[57] was done according to the literature.

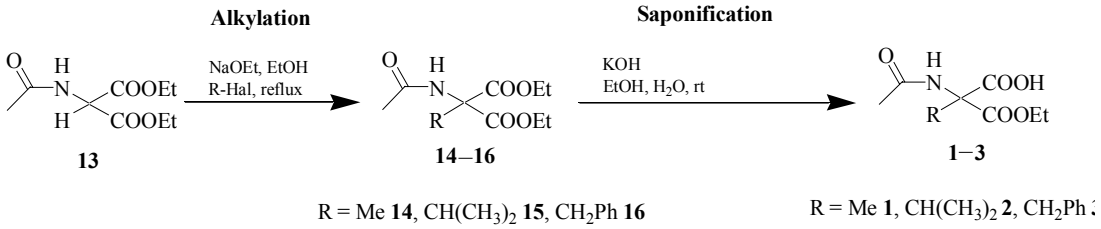


Figure 21: *Alkylation of precursor diethyl 2-N-acetylaminomalonate **13***

In the second step, the alkylated malonates **14**, **15** and **16** were partially saponified with KOH in aqueous ethanol at room temp. to obtain hemiesters **1**[58], **2** and **3**[59].

Furthermore it was attempted to obtain 2-*N*-acetylamino-2-ethoxycarbonyl-2-phenylacetic acid. But the saponification of the corresponding diethylester always arrived at the decarboxylation product ethyl *N*-acetylphenylglycinate. Therefore, it seems that the free acid is not stable.

3.2.2 Synthesis of α-fluorinated β-keto esters

3.2.2.1 Synthesis of benzyl β-keto esters

For the catalysis leading to α-fluoro ketones, benzyl ß-keto esters were synthesised which were then fluorinated.

The linear β-ketoester 3-oxo-2,3-diphenyl-propionic acid benzyl ester **19**[30] was prepared in two steps (Figure 22). In the first step, ester **18**[30] was formed from phenylacetic acid **17** by reaction with benzyl bromide. The benzoylation of this ester was done using the base BuLi/hexamethyldisilazane (HMDS).

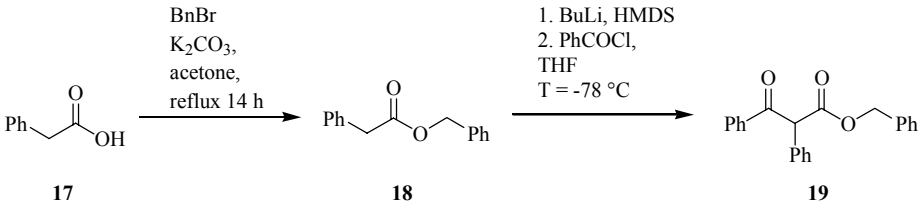


Figure 22: *Synthesis of the linear benzyl ester **19***

The cyclic ethyl β-keto esters **21**[60] and **24**[23] were prepared by Claisen condensation, starting from cyclohexanone **20** and 1-tetralone **23** which were treated with NaH and a large excess of diethyl carbonate (Figure 23).

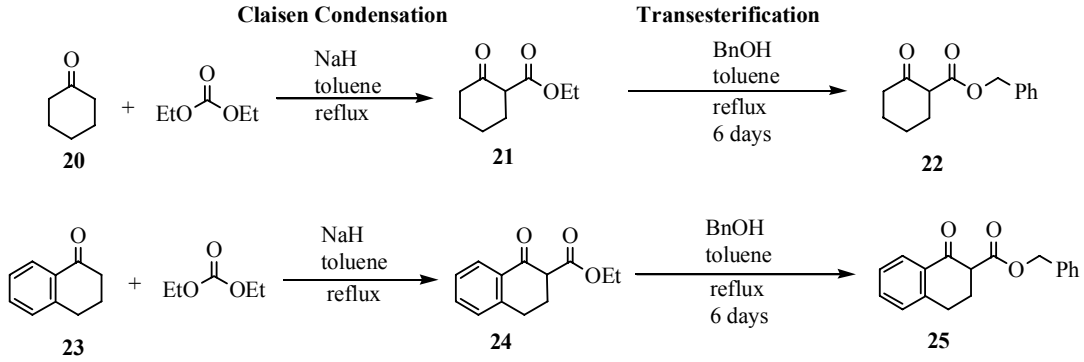
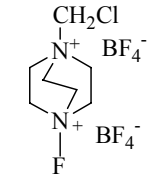


Figure 23: *Preparation of the cyclic benzyl ß-keto esters **22** and **25***

To obtain the desired benzyl esters **22** and **25**, the ethyl esters **21** and **24** were transesterified (Figure 23) analogous to literature procedures[61]. The reaction was carried out without acid or base, just refluxing the ß-keto ester with an excess of benzyl alcohol in toluene.

3.2.2.2 Fluorination of β-keto esters

The first reagents used for electrophilic fluorination of carbanions were perchlorylfluoride $FClO_3$, xenon difluoride, XeF_2 and hypofluorites[62]. But these fluorination reagents have some disadvantages: only moderate selectivity, quite expensive and dangerous to use as they are powerful oxidants for organic compounds.
Nowadays available organic N−F fluorinating agents for electrophilic fluorination have the advantage that they are solid, more or less stable and easy to handle. There are different classes commercially available, e.g. *N*-fluoropyridinium salts[63], *N*-fluorobenzenesulfonimides[64] and 1,4-diazabicyclo[2.2.2]octane salts[65]. From the last group mentioned, a quite low-priced one which became popular recently is Selectfluor™ (Figure 24), available from Aldrich company.

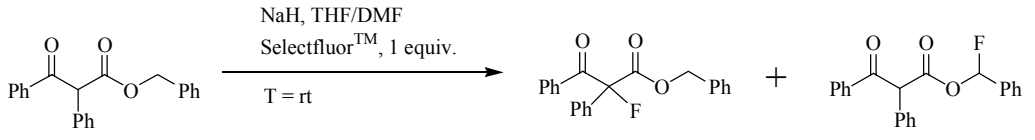


Selectfluor™

1-(chloromethylene)-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane-bis-tetrafluoroborate

Figure 24: *The electrophilic fluorination reagent Selectfluor™*

The electrophilic fluorination of the linear product **19** with Selectfluor™ was first attempted under neutral conditions analogous to the literature[66], but under these conditions there was no fluorination. Trying another instruction[67], under basic conditions (solvent: THF/DMF, base: NaH) the fluorination worked (Figure 25). The byproduct **26** with the fluorinated benzyl position is visible in the ^{19}F and ^{1}H NMR spectra. The chromatographed product **7** was always contaminated with at least 3% of byproduct **26**.



19 **7** **26**

Figure 25: *Electrophilic fluorination of linear compound **19***

In contrast to the linear compound **19,** the fluorination of the cyclic ß-keto esters **22** and **25** worked smoothly under neutral conditions analogous to the literature (Figure 26) [66].

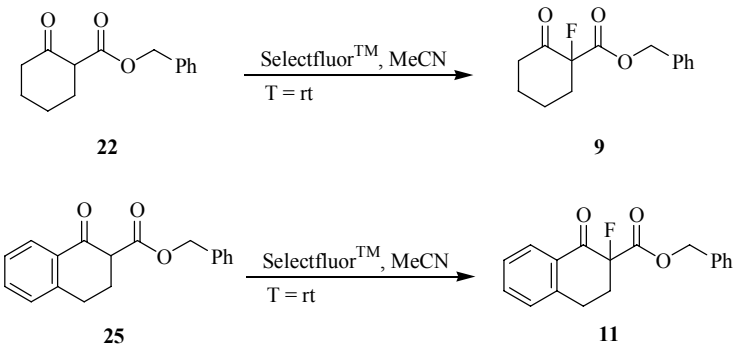


Figure 26: *Fluorination of cyclic compounds **22** and **25***

3.2.3 Synthesis of 2-fluoro-1-tetralol

2-Fluoro-1-tetralol was found as a byproduct in the decarboxylation of benzyl 2-fluoro-1-tetralone-2-carboxylate **11**. It was synthesised in order to have it in a sufficient amount and puritity to establish analysis and quantitative HPLC. Therefore, 2-fluoro-1-tetralone **12** was reduced with $NaBH_4$ to obtain the desired alcohol **27** (Figure 27) [68].

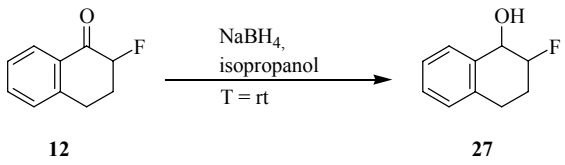


Figure 27: *Synthesis of 2-fluoro-1-tetralol **27***

3.3 Synthesis of the catalysts

3.3.1 Synthesis of amides of 9-amino(9-deoxy)epicinchonine

The amides were prepared in two steps (Figure 28). In the first step, 9-amino(9-deoxy)epicinchonine **29**[51] was prepared from cinchonine **28** *via* a Mitsunobu reaction leading to an inversion at C9. Amine **29** was then converted to amides **30**–**40** using the appropriate acid chlorides analogous to the literature[25]. Amides **30**, **31** (ref. 51) and **32**–**35** (ref. 25) are known.

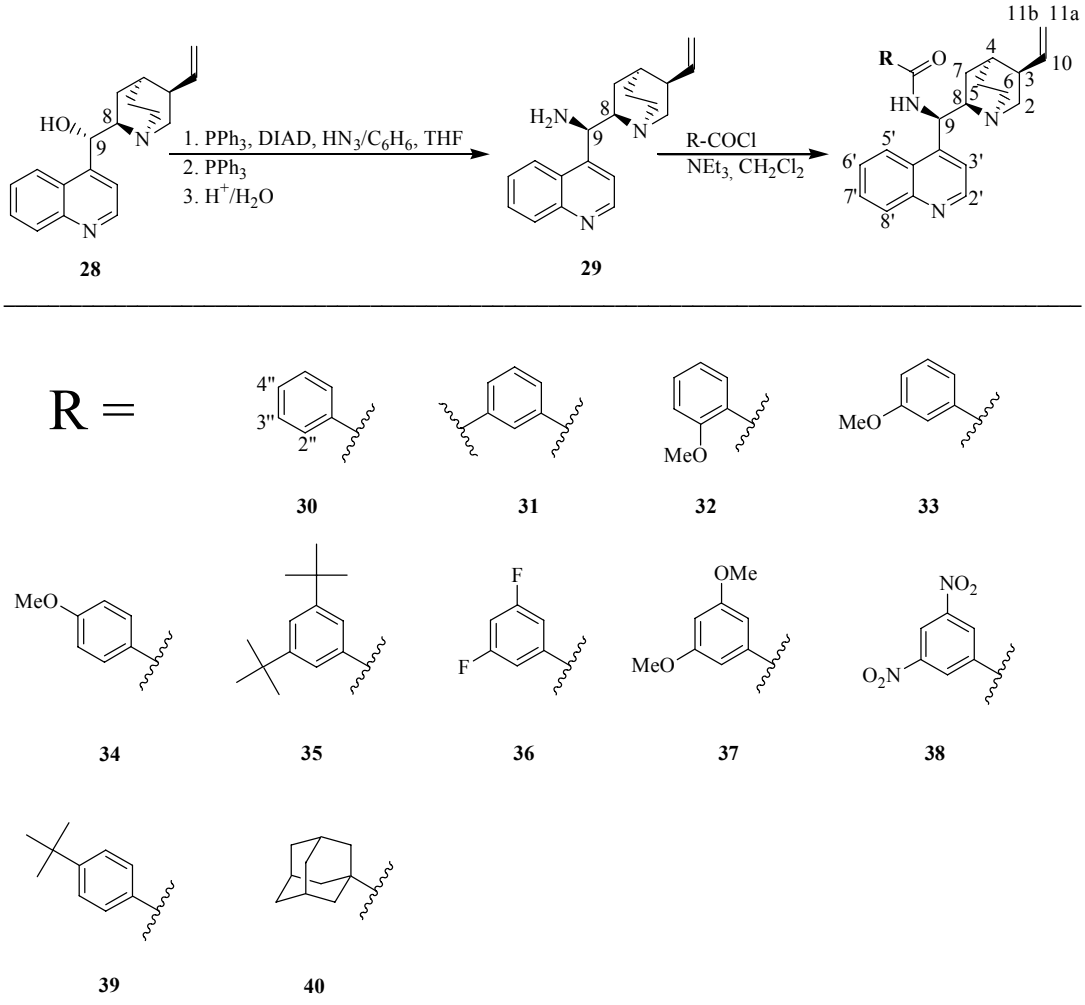


Figure 28: *Preparation of amides* ***30–40***

3.3.2 Further derivatives

Besides carboxylic acid amides, further derivatives have been synthesised. For two of these derivatisations, 3,5-di-*tert*-butylbenzenesulfonyl chloride **42**[69] was used. It was derived by ipso-substitution of 1,3,5-tri-tert-butylbenzene which was treated with chlorosulfonic acid (Figure 29).

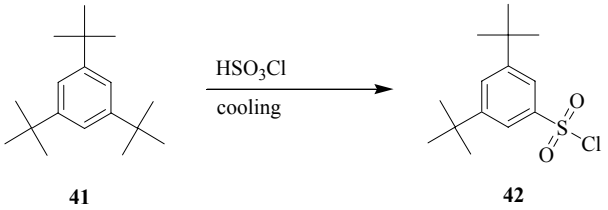


Figure 29: *Preparation of 3,5-di-tert-butylbenzenesulfonyl chloride* ***42****.*

3.3.2.1 Derivatives of 9-amino(9-deoxy)epicinchonine

The amino group of **29** was derivatised in a couple of ways. Structurally familiar to the carboxylic acid amides, sulfonamides **43** and **44** were prepared (Figure 30) [70]. *N*-(9-Deoxyepicinchonine-9-yl)-2,4-dinitrophenylamine **45** was synthesised by nucleophilic aromatic substitution with Sangers reagent 2,4-dinitrofluorobenzene. Another derivatisation of the amino group of **29** was carried out with phenylisocyanate, arriving at *N*-(9-deoxyepicinchonine-9-yl)-*N'*-phenylurea **46**.

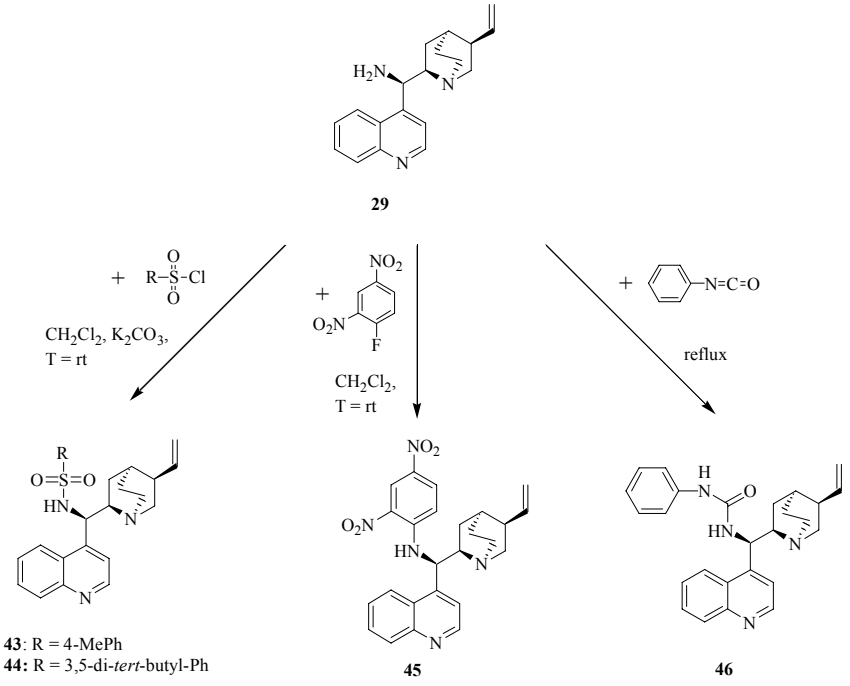


Figure 30: *Preparation of sulfonamides* ***43*** *and* ***44****, amine* ***45*** *and urea derivative* ***46***

3.3.2.2 Derivatives of cinchonine

The hydroxy group of cinchonine **28** was derivatised with phenylisocyanate obtaining cinchonine-9-yl phenylcarbamate **47**[71] (Figure 31). Cinchonine-9-yl-3,5-di-*tert*-butylbenzenesulfonate **48** was prepared analogous to a described tosylation[51].

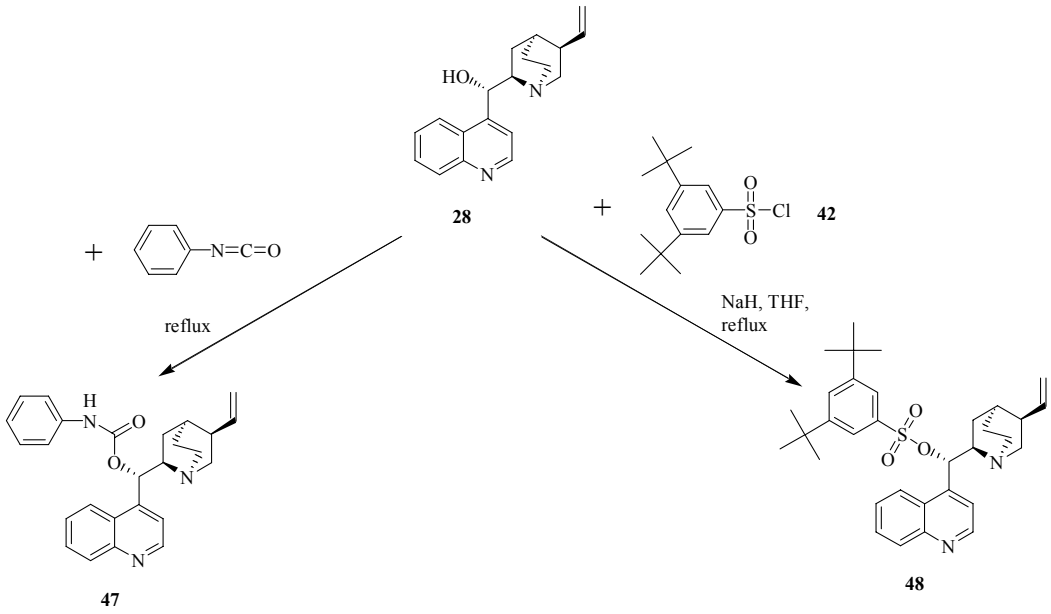


Figure 31: *Preparation of carbamate **47** and sulfonate **48***

3.3.2.3 Derivative of quinidine

The intramolecular ether ß-isocupreidine **50**[72] was formed in one step by refluxing quinidine **49** in concentrated H_3PO_4 with KBr (Figure 32). This derivative proved to be a successful catalyst in the Baylis Hillmann reaction.

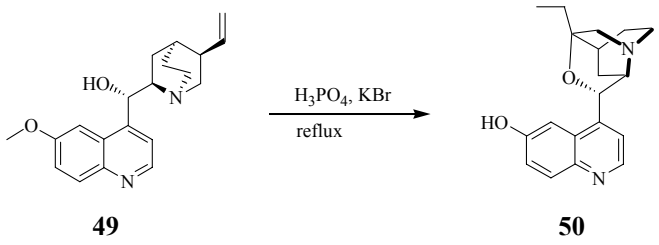
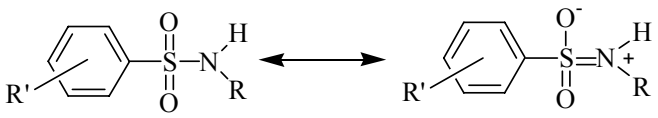


Figure 32: *Synthesis of ß-isocupreidine **50***

3.3.3 ^{1}H NMR analytics

The sulfonamides **43** and **44** gave unexpectedly complicated ^{1}H NMR spectra in $CDCl_3$ at room temp. Signals which belong to one proton splitted in two signals with a ratio of 1 to 0.4. The reason for this phenomenon is the hindered rotation around the S-N bond due to a partial double bond character (Figure 33). Usually, the elements of the third and higher periods exhibit much lower tendencies to π-bonding. Therefore, the rotation barriers



R = *N*-(9-Deoxyepicinchonine-9-yl)

Figure 33: *Resonance forms of benzene-sulfonamide moiety*

in the sulfonamides should be much lower than those of the carboxylic amides. In contrast to that, the sulfonamides **43** and **44** of 9-amino(9-deoxy)epicinchonine showed hindered rotation in ^{1}NMR, while the familiar carboxyl amides do not. The phenomenon of hindered rotation about S-N bonds was recently reported for *N*,*N*-disubstituted sulfonamides[73,74]. With *N*-(9-deoxyepicinchonine-9-yl)-4-methylbenzenesulfonamide **43** a ^{1}H NMR spectra in $C_2D_2Cl_4$ was recorded in the temperature range from 27–115 °C (Figure 34). At 27 °C it can be seen that not only the protons of 4-methylbenzene (normally an AA´BB´ spectra) are affected from the slow exchange, but also the protons of the quinoline ring. It is observable that there is coalescence at 80 °C with broad peaks. At 110 °C the exchange is fast enough to sharpen the signals and interpretation can be done analogous to the carboxylic amide derivatives. A comparison between the spectra of sulfonamide **43** and the corresponding benzamide **39** shows the analogy of the spectra (Figure 35). The three signals with the highest δ values in the low field region belong to the quinoline ring protons H2', H5' and H8'. The amide proton NH gives a broad signal which is not always visible. Characteristic from their appearance and location are the multiplets of H6' and H7'. The signal of H3' is the one with the lowest δ value of the quinoline protons. For both substances, the AA'BB' system of H2''/H6'' and H3''/H5'' of the *para*-substituted

benzene residue is obvious. Typical for all cinchona alkaloid derivatives are the ddd signal of H10 and the two pseudo-triplets of doublets for H11. The coupling pattern of H11 arises from the coupling with H10, H3 and the other geminal H11 proton. As the geminal coupling with the other H11 proton and the long-range coupling with H3 have the same values, the signal of H11 appears as a pseudo-triplet of doublet. Due to dynamic effects, the signal of H9 is very broad. Because of their proximity to the electronegative nitrogen, the protons H2, H6 and H8 are those with the highest ppm values of the quinuclidine framework. Proton H3 always shows up as a single multiplet. Protons H4, H5 and H7a mostly overlap to one multiplet. The signal with the highest shift is the one of H7b.

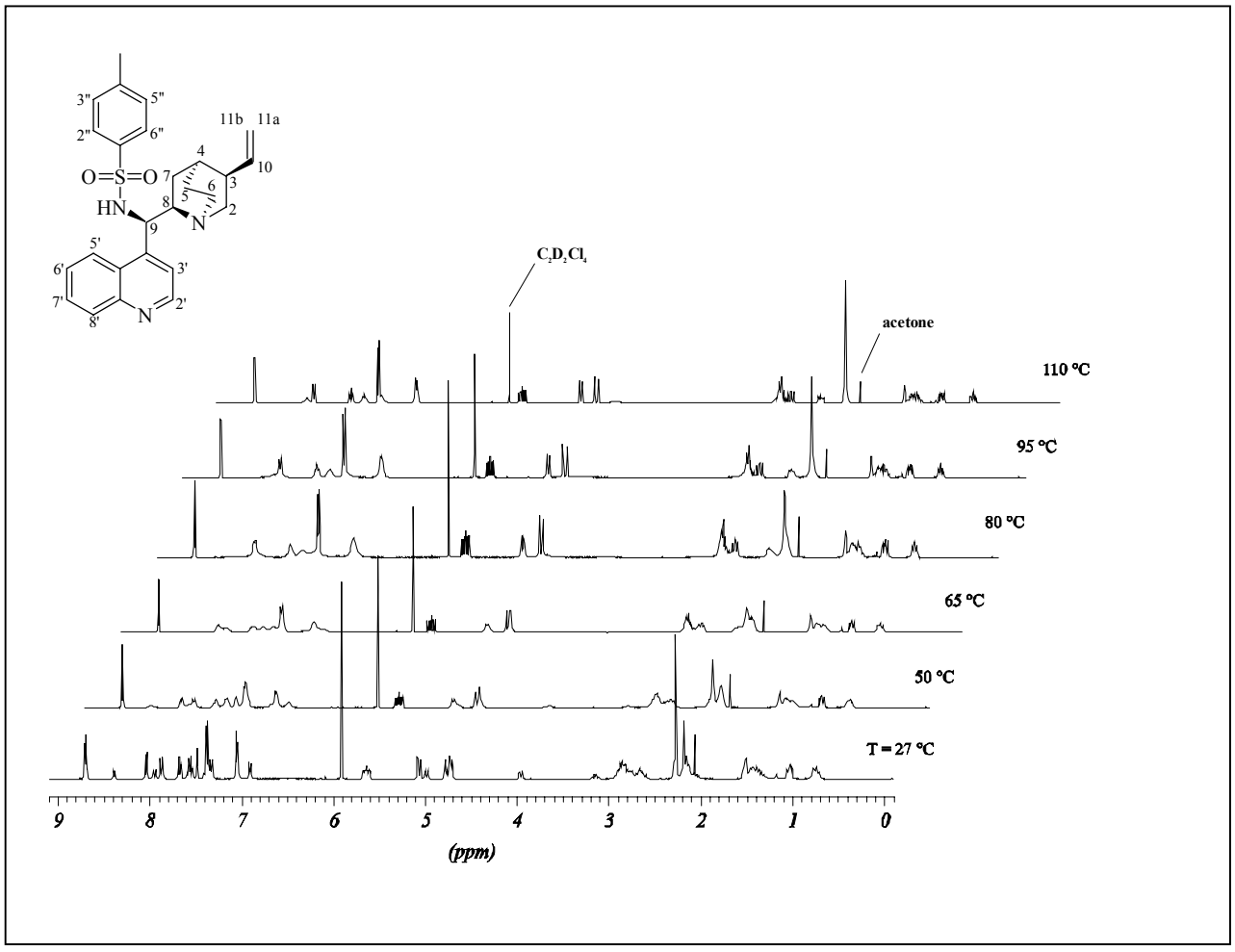


Figure 34: *Coalescence spectra of N-(9-deoxyepicinchonine-9-yl)-4-methylbenzene-sulfonamide* ***43***

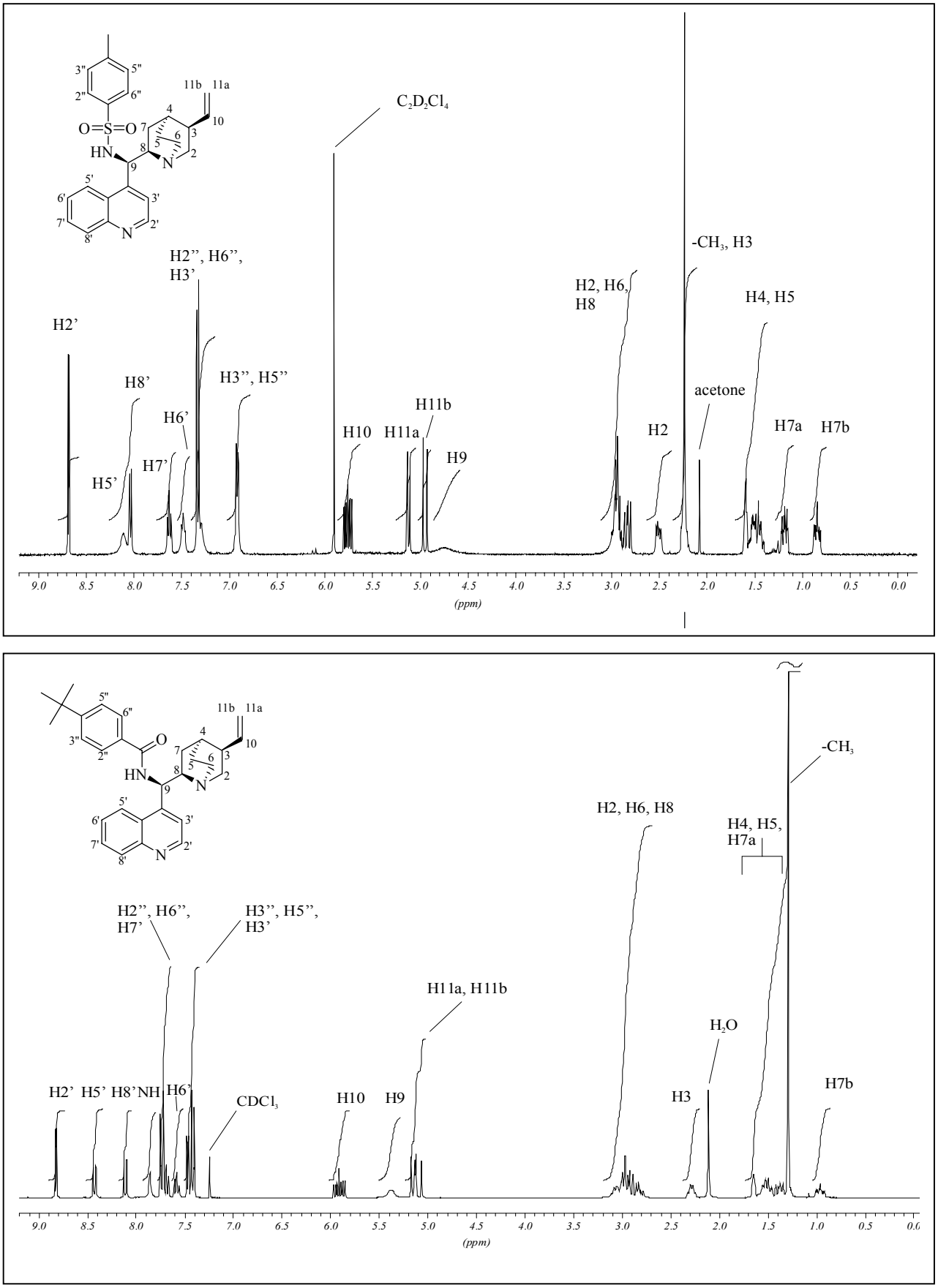


Figure 35: *[1]H NMR of sulfonamide **43** (400 MHz, $C_2D_2Cl_4$, 110 °C) and carboxylamide **39** (300 MHz, $CDCl_3$, 27 °C)*

4 Catalysis

4.1 Overview on the applied catalysts

In addition to the already introduced self-synthesised catalytically active bases, further derivatives have been tested. Therefore, all catalysts employed in the different catalytic systems described in this chapter are displayed in Figure 36 and 37. The commercial cinchona alkaloids were purchased from Merck and Fluka. Amide derivatives **53**[32] and **54–63**[25] were available from previous studies.

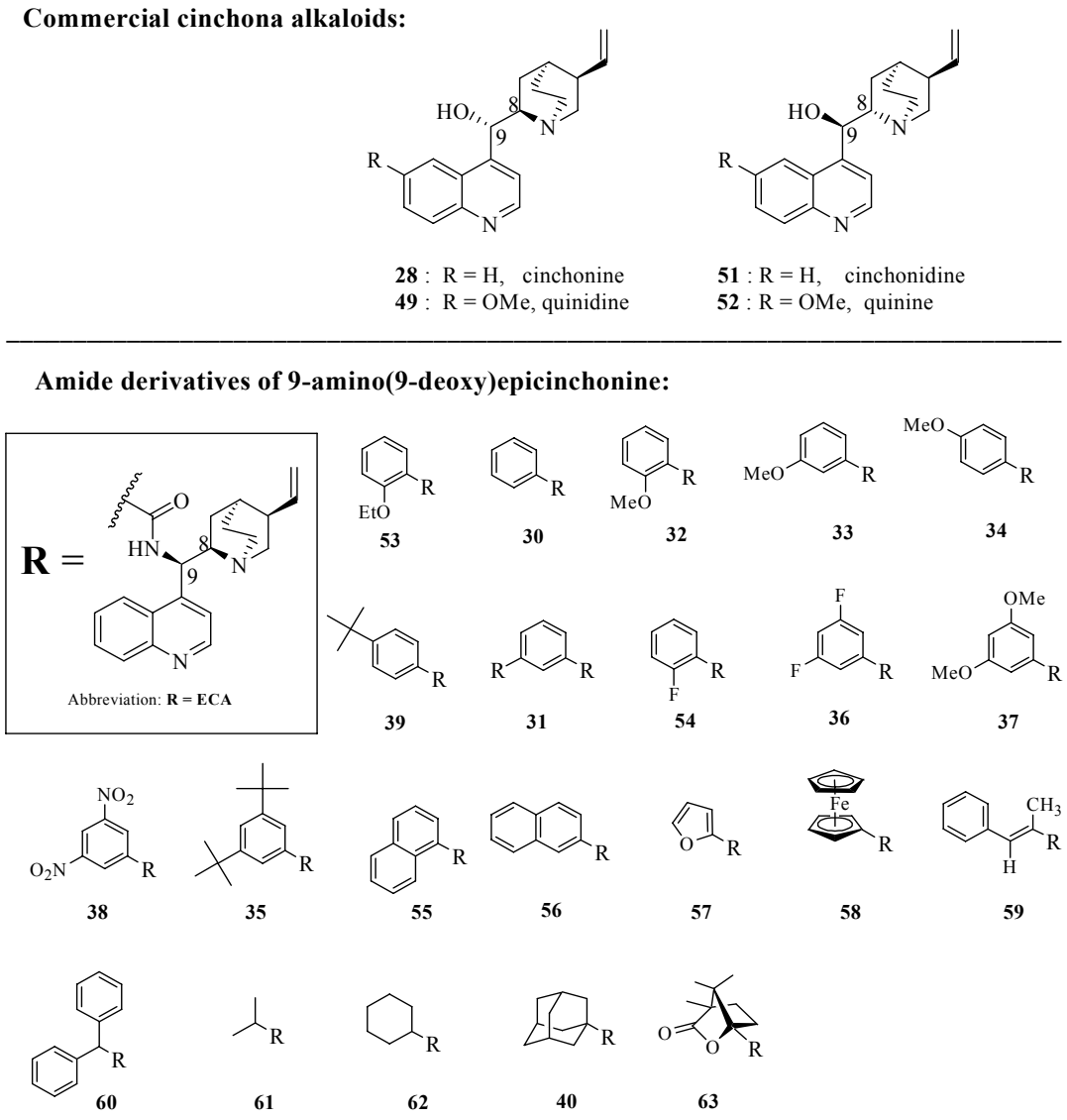
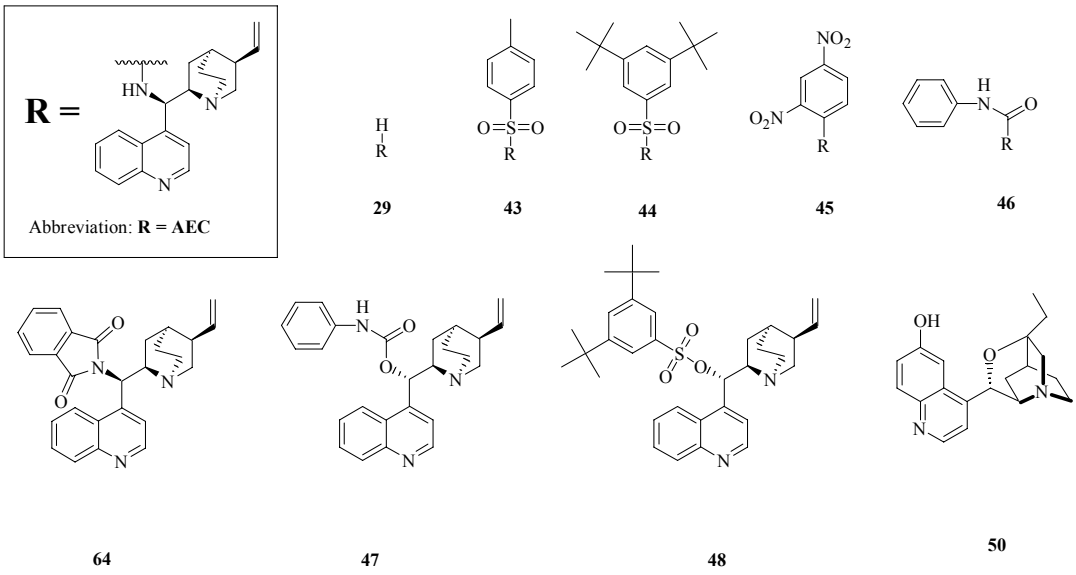


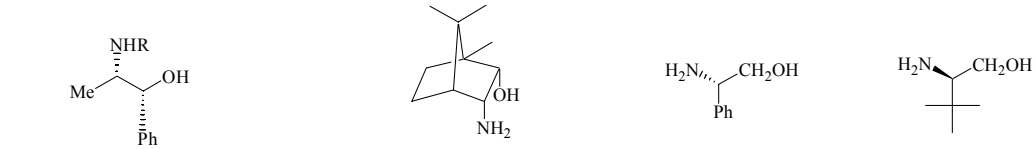
Figure 36: *Commercial cinchona alkaloids and amide derivatives of 9-amino(9-deoxy)epicinchonine*

Further already available catalysts were **64**[25], **67**[30] and **68**, **69**[75]. (-)-Ephedrine **65** and (-)-norephedrine **66** were purchased from Acros.

Further cinchona alkaloid derivatives:



ß-Aminoalcohols:



65 R = Me: (1*R*, 2*S*)-(-)-ephedrine
66 R = H: (1*R*, 2*S*)-(-)-norephedrine

67 (+)-endo-2-hydroxy-endo-3-aminobornane

68 (*R*)-(-)-phenyl-glycinol

69 (*S*)-(+)-*tert*-leucinol

Figure 37: *Further cinchona alkaloid derivatives and ß-aminoalcohols*

For easier reading of the tables, the residues of the *N*-(9-deoxyepicinchonine-9-yl)amide derivatives was abbreviated with ECA (Figure 36), the 9-amino(9-deoxy)epicinchonine residue with AEC (Figure 37).

4.2 Enantioselective decarboxylation leading to α-amino acid derivatives

While there are many asymmetric syntheses leading to enantiopure α-amino acids,[76,77] examples for catalytic enantioselective decarboxylation are rare, not taking into account enzymatic decarboxylation reactions. An approach was made with *trans*-dichloro cobalt(III) complexes, which needed stoichiometric amounts of the complex. Furthermore, the procedure was quite complicated[78,79,80]. In contrast, the catalysis described here only needs substoichiometric amounts of catalyst and is easy to carry out.

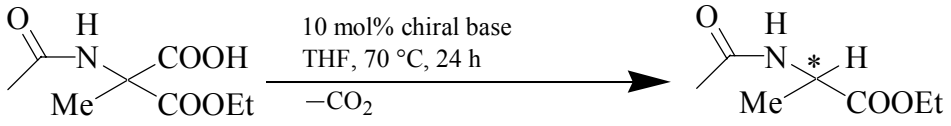
4.2.1 General standard procedure

The racemic 2-***N***-acetylamino-2-alkylmalonic acid monoethyl esters **1**–**3** (0.74 mmol) and 10 mol% optically active base were stirred in 9 mL abs. THF at 70 °C under nitrogen. After 24 h the reactions were stopped by cooling and evaporating the solvent at room temp. The residue was dissolved in diluted hydrochloric acid and extracted with ethyl acetate. The base stayed in the water phase and could be recycled. The organic layer was evaporated and the conversion was determined by ^{1}H NMR spectroscopy. Usually, conversion was quantitative.

4.2.2 The alanine system

4.2.2.1 First testings

The optimum conditions for this system, a reaction temperature of 70 °C and THF as solvent, have been elaborated in my previous work[32]. Furthermore, hemiester **1** had turned out to be the best substrate. The diacid 2-*N*-acetylamino-2-methylmalonic acid and the nitrile derivative 2-*N*-acetylamino-2-cyanopropionic acid had given poor results in first testings. Therefore, 2-*N*-acetylamino-2-ethoxycarbonylpropionic acid **1** was chosen as substrate further testings.



1 **4**

Figure 38: *Decarboxylation leading to ethyl N-acetylalaninate **4***

The results with the commercial cinchona alkaloids **28**, **49**, **51** and **52** under standard conditions are given in entries 1–4 of Table 1. Obviously, the configurations at positions 8 and 9 of the cinchona alkaloid and the prescence or absence of the methoxy group in 6'-position of the quinoline ring determine the direction of induction. With respect to positions 8 and 9, cinchonine **28** and cinchonidine **51** as well as quinidine **49** and quinine **52** are mirror image isomers. Consequently, cinchonine **28** and cinchonidine **51** (entries 1 and 2) as well as quinidine **49** and quinine **52** (entries 3 and 4) gave different configurations of product **4**. On the other hand, the pairs cinchonine **28**/quinidine **49**

Table 1: First tested catalysts (THF, T = 70 °C, t = 24 h, 100% conversion)

Entry	Base (10 mol%)	ee [%] of 4	configuration
1	cinchonine **28**	9.6; 9.0; 9.0	D
2	cinchonidine **51**	4.8; 5.0	L
3	quinidine **49**	4.2; 4.0	L
4	quinine **52**	5.6; 6.2	D
5	2-EtO-Ph-ECA **53**	18.4; 18.6	L

and cinchonidine **51**/quinine **52** have the same configurations at position 8 and 9. They just differ in the absence or presence of a methoxy group in the quinoline system. Surprisingly, the components of the pairs afforded opposite configurations in product **4**. *N*-(9-Deoxyepicinchonine-9-yl)-2-ethoxybenzamide (**53**), the best base in the Naproxen® system[25,26], gave better enantioselectivities than the commercially available alkaloids (entry 5).

4.2.2.2 Screening of bases

Since benzamides of the cinchona alkaloids had been the best bases in decarboxylation reactions of the Naproxen® system[25,26], in addition to benzamide **53**, further amides were screened as catalysts in the decarboxylation of hemiester **1**.

In the decarboxylation of hemiester **1** to the acetylated alanine ester **4**, the unsubstituted benzamide **30** gave promising results with about 50% ee (Table 2, entry 1). The *ortho*-, *meta*- and *para*-methoxy substituted benzamides **32**–**34** were tested to see whether there were steric and electronic effects. In fact, the *ortho*-substituted derivative **32** afforded only about 18% ee (entry 2) compared to the *meta*- and *para*-substituted derivatives **33** and **34** with about 52% ee (entries 3 and 4) indicating steric hindrance of *ortho*-substituents. This was corroborated by the low enantioselectivities of the *ortho*-ethoxy derivative **53** and the *ortho*-fluoro derivative **54** (Table 1, entry 5; Table 2, entry 7).

Table 2: Testing of amide derivatives (THF, T = 70 °C, t = 24 h, 100% conv.)

Entry	Base (10 mol%)	ee [%] of 4, L-config.
1	Ph-ECA **30**	48.2; 51.6
2	2-MeO-Ph-ECA **32**	16.7; 19.3
3	3-MeO-Ph-ECA **33**	52.0; 52.2
4	4-MeO-Ph-ECA **34**	49.9; 52.2
5	4-*tert*-butyl-Ph-ECA **39**	53.9; 54.2
6	3-ECA-Ph-ECA **31**	43.8; 44.4
7	2-F-Ph-ECA **54**	26.5; 29.6
8	3,5-di-F-Ph-ECA **36**	53.9; 54.2
9	3,5-di-MeO-Ph-ECA **37**	52.1; 53.7
10	3,5-di-NO_2-Ph-ECA **38**	49.6; 50.8
11	3,5-di-*tert*-butyl-Ph-ECA **35**	58.0; 59.6
12	1-naphtyl-ECA **55**	29.3; 35.7
13	2-naphtyl-ECA **56**	44.1; 39.9
14	2-furanyl-ECA **57**	44.5;46.7
15	ferrocenyl-ECA **58**	53.2; 54.0
16	α-methylcinnamic-ECA **59**	42.3; 49.8
17	1,1-di-Ph-CH-ECA **60**	24.6; 26.8
18	isopropyl-ECA **61**	24.5; 24.7
19	cyclohexyl-ECA **62**	24.0; 25.8
20	adamantyl-ECA **40**	8.0; 6.0
21	(1*S*)-camphane-ECA **63**	4.2; 4.9

39 with a *tert*-butyl group in *para*-position gave 54% ee (entry 5) and the dibenzamide **31** 44% ee (entry 6). Compounds **36**, **37**, **38**, containing strongly electron-withdrawing and electron-attracting substituents in 3,5-position led to an enantiomeric excess in a range between 50 and 54% ee (entries 8–10), showing that there was no pronounced inductive effect. *N*-(9-Deoxyepicinchonine-9-yl)-3,5-di-*tert*-butylbenzamide (**35**) afforded the best result (59% ee) in this series (entry 11).

As expected on the basis of the steric hindrance argument, the 1-naphthyl derivative **55** gave a lower ee than the 2-naphthyl derivative **56** (entries 12 and 13). The 2-furanylamide **57** and the ferrocenylamide **58** provided similar results as the parent benzamide **30** (entries 14 and 15).

Amides lacking the aromatic substituent were much less efficient in the decarboxylation of **1**. While the α-methylcinnamic acid amide **59** yielded about 45% ee (entry 16), the aralkyl and alkyl derivatives **60**–**63** and **40** afforded only low enantioselectivities (entries 17–21) including the adamantane derivative **40** and the (1*S*)-(–)-camphanic acid derivative **63** in which even group R was chiral.

In addition, further cinchona alkaloid derivatives **43**–**48**, **64** and **50** were tested in the decarboxylation of hemiester **1**. Similar to the phenyl- and di-*tert*-butylphenyl-substituted benzamides **30** and **35**, the corresponding sulfonamides **43** and **44**, derived from 9-amino(9-deoxy)epicinchonine (**29**), afforded 55 and 52% ee (Table 3, entries 1 and 2).

Table 3: Decarboxylation of **1** with cinchona alkaloid derivatives **43**–**48**, **64** and **50** (THF, T = 70 °C, t = 24 h, 100% conversion)

Entry	Base (10 mol%)	ee [%] , L-config.
1	tosyl-AEC **43**	53.9; 55.6
2	3,5-di-tert-butyl-Ph-SO_2-AEC **44**	51.0; 52.7
3	2,4-di-fluoro-Ph-AEC **45**	2.5; 3.6
4	phthalimide-AEC **64**	0.8; 2.4
5	PhNHCO-AEC **46**	28.2; 32.5
6	PhNHCO-cinchonine **47**	17.2; 18.0
7	3,5-di-tert-butyl-Ph-SO_2-cinchonine **48**	6.5; 6.7
8	ß-isocupreidine **50**	20.4; 22.1

Amine **45** and phthalimide **64** gave poor results (entries 3 and 4), whereas the urea derivative **46** led to 30% ee (entry 5). The carbamate and sulfonate esters **47** and **48** of cinchonine achieved only low enantioselectivities as did ß-isocupreidine **50** (entries 6, 7 and 8).

4.2.2.3 Further variations

With **53**, the effect of varying the amount of catalyst in the decarboxylation of hemiester **1** was tested (Table 4, entries 1–8). Increasing the amount of **53** gave rise to an increase of the enantiomeric excess, reaching 41.5% ee with 60 mol% base (entry 7). Use of a stoichiometric amount of base did not change the results (entry 8). In contrast, with **35** the enantiomeric excess could not be improved with higher amounts of base (entries 9 and 10). Interestingly, with 60 mol% of the 3,5-di-methoxy substituted amide **37** and the 3-methoxy substituted benzamide **33** enantiomeric excess increased to about 66 % (entry 11 and 12). A decrease of the reaction temperature to 30 °C with base **35** made the reaction sluggish. After 18 days there was only 85% conversion with decreased enantioselectivity (entry 13).

Table 4: Variation of catalyst concentration and temperature in the decarboxylation of **1→4** (100% conversion except for entry 13: 85%)

Entry	Base	mol% base	T [°C]	t [h]	ee [%] of 4, L-config.
1	2-EtO-Ph-ECA **53**	5	70	24	8.1
2	**53**	10	70	24	18.5
3	**53**	20	70	24	23.5
4	**53**	30	70	24	27.7
5	**53**	40	70	24	31.2
6	**53**	50	70	24	34.4
7	**53**	60	70	24	41.5
8	**53**	100	70	24	42.4
9	3,5-di-*tert*-butyl-Ph-ECA **35**	30	70	24	62.8
10	**35**	60	70	24	60.2
11	3,5-di-MeO-Ph-ECA **37**	60	70	24	65.9
12	3-MeO-Ph-ECA **33**	60	70	24	65.5
13	3,5-di-*tert*-butyl-Ph-ECA **35**	10	30	432	53.6

4.2.2.4 Kinetic study

A kinetic study of the decarboxylation of **1** was performed with base **27**, which had been the most successful catalyst in the system **1→4**. The twelvefold standard reaction was analyzed taking samples each hour. Conversion was almost complete after 12 hours (Figure 39). At the beginning of the catalysis the enantiomeric excess of ethyl *N*-acetylalaninate (**4**) was a little lower. After 5 h it reached 60% ee and stayed constant then. A similar observation had been made in the Naproxen® system[25]. This is in contradiction to a recently published computational study[53], denying a two-step

decarboxylation/protonation mechanism and suggesting a concerted mechanism according to which each enantiomer of the starting material transforms into its own product enantiomer. In such a case, kinetic resolution should occur. This was not

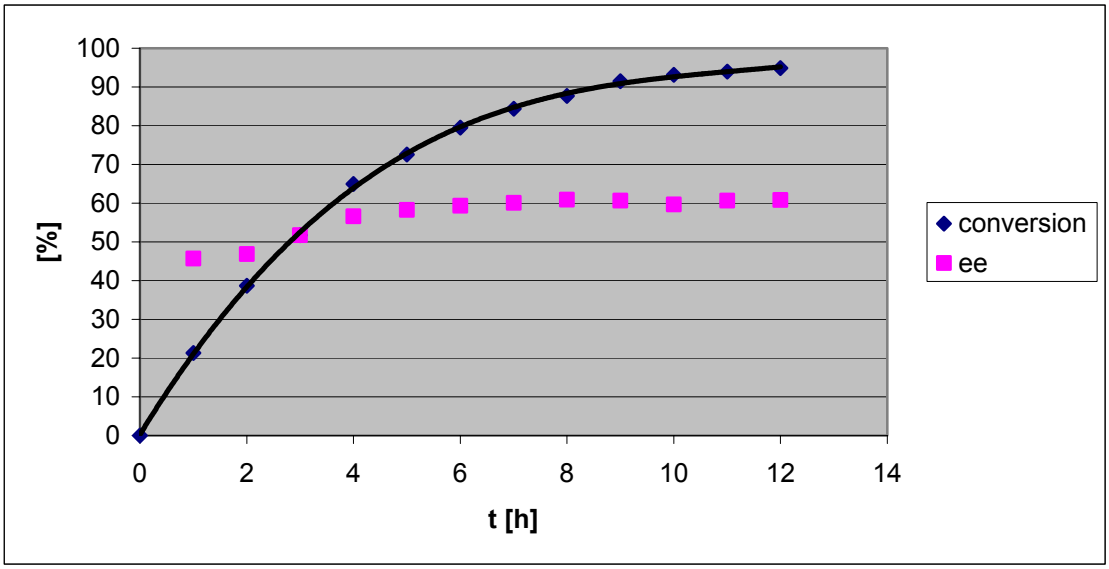
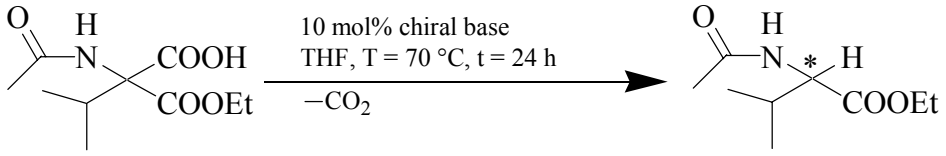


Figure 39: *Kinetics of the decarboxylation of* ***1→4*** *with base* ***35***

observed, neither in the Naproxen® system[25] nor in the present study. Moreover, in the Naproxen® system it had been shown that both enantiomers of the resolved starting material 2-cyano-2-(6-methoxynaphth-2-yl)propionic acid gave the same product enantioselectivity of about 68% ee, which is incompatible with a concerted mechanism. Therefore, the two-step decarboxylation/protonation mechanism *via* planar intermediates, such as the enolate of ethyl *N*-acetylalaninate in the decarboxylation of **1**, and their stereoselective protonation, is plausible.

4.2.3 The valine system

The screening was extended to the decarboxylation of **2** affording valine derivative **5** (Figure 40). With the unsubstituted benzamide **30** 15% ee was obtained (Table 5, entry 1). Again the *ortho*-methoxy-substituted base **32** gave a bad result, in this case a racemate (entry 2), whereas the *meta*- and *para*-derivatives **33** and **34** matched the unsubstituted benzamide **30** with about 13% ee (entries 3 and 4).



2 **5**

Figure 40: *Decarboxylation leading to ethyl N-acetylvalinate*

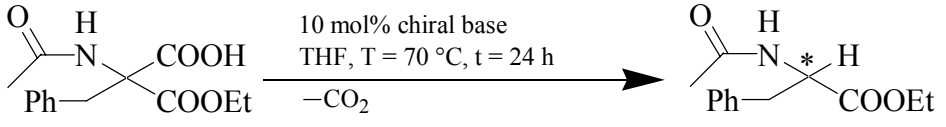
An increase to 48% enantiomeric excess was observed with *N*-(9-deoxyepicinchonine-9-yl)-2,5-di-*tert*-butylbenzamide (**35**) (entry 5), also the best base in the system **1**→**4**.

Table 5: Decarboxylation of **2** with different bases (THF, T = 70 °C, t = 24 h, 100% conversion)

Entry	Base (10 mol%)	ee [%] of 5, L-config.
1	Ph-ECA **30**	14.2; 15.6
2	2-MeO-Ph-ECA **32**	*rac.*
3	3-MeO-Ph-ECA **33**	9.7; 13.2
4	4-MeO-Ph-ECA **34**	11.8; 13.7
5	3,5-di-*tert*-butyl-Ph-ECA **35**	48.0

4.2.4 The phenylalanine system

Enantioselectivities were generally high in the decarboxylation of **3** to give ethyl *N*-acetylphenylalaninate **6**. The unsubstituted benzamide **30** afforded 67% ee (Table 6, entry 1). Again, the *ortho*-substituted methoxybenzamide **32** gave only 38% ee (entry



3 **6**

Figure 41: *Decarboxylation leading to ethyl N-acetylphenylalaninate*

2), whereas the *meta*- and *para*-substituted methoxybenzamides **33** and **34** achieved 65% and 70% ee (entries 3 and 4). With **39** and **35** close to 70% ee were obtained (entries 5 and 6). The sulfonamides **43** and **44** resulted in 63% and 65% ee (entries 7 and 8).

Table 6: Decarboxylation of **3** with different bases (THF, T = 70 °C, t = 24 h, 100% conversion)

Entry	Base (10 mol%)	ee [%] , L-config.
1	Ph-ECA **30**	65.7; 69.0
2	2-MeO-Ph-ECA **32**	37.1; 37.8
3	3-MeO-Ph-ECA **33**	63.7; 65.4
4	4-MeO-Ph-ECA **34**	69.3; 71.1
5	4-tert-butyl-Ph-ECA **39**	67.3; 69.1
6	3,5-di-*tert*-butyl-Ph-ECA **35**	65.8; 67.7
7	tosyl-AEC **43**	62.4; 63.6
8	3,5-di-tert-butyl-Ph-SO_2-AEC **44**	64.1; 64.7

4.2.5 Analytics

Conversion was monitored with TLC (SiO_2) using EtOAc as eluent. Compounds **1**–**6** were made visible by heating with molybdatophosphoric acid (for **3** and **6** UV worked also). For exact conversion control by ^{1}H-NMR, the singlet of the acetyl group of the starting material was compared to that of the product (data see experimental part). Samples with incomplete conversion have to be chromatographed on SiO_2 with EtOAc in order to remove the starting material.

The determination of the enantiomeric excess in the decarboxylation of 2-*N*-acetylamino-2-alkylmalonic acid ethyl esters was achieved with gaschromatography. With a chiral capillary column all enantiomers can be separated. An exact baseline separation was possible. Repeated injections gave similar results. The enantiomeric excess can be calculated from the peak areas A:

$$ee[\%] = 100 \times \frac{|A_R - A_S|}{A_R + A_S}$$

For example, Figure 42 shows a cutout of the chromatogram of the catalysis leading to ethyl *N*-acetylphenylalaninate **6**. The area ratio corresponds to an enantiomeric excess of 62.4% ee. The signal with the longer retention time was assigned to the L enantiomer by optical rotation measurements of an enantiomerically enriched sample of **6**[81].

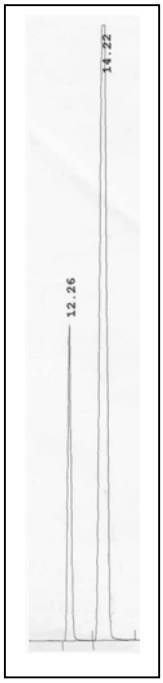


Figure 42: *GC cutout of a sample of* ***6*** *with 62.4% ee*

4.3 Enantioselective decarboxylation leading to α-fluoro ketones

The synthesis of cyclic and acyclic chiral fluoro-organic compounds is an important topic in modern pharmaceutical and agricultural chemistry[82,83]. Furthermore, chiral α-fluoro ketones are useful for the asymmetric epoxydation of alkenes[84]. The generation of quaternary stereogenic fluoro centres in carbonyl α-position is now well developed, but at least a stoichiometric amount of a chiral fluorinating agent[85,86,87,88,89] or chiral substrate is required[90]. Catalytic methods consist of asymmetric alkylation of racemic α-fluoro carbonyl compounds under phase-transfer conditions[91,92,93] and fluorination of ß-keto esters activated by chiral Lewis acid-TADDOL-complexes[94] or in the presence of chiral palladium complexes[95]. The enantioselective formation of a tertiary fluoro centre α to a carbonyl group is problematic since most of the above methods work in media which are not neutral enough to avoid racemisation of the newly fluorinated carbon with enhanced acidity. Thus, only strategies starting from compounds having chiral protective groups are available for this purpose[96,97].

The employment of the palladium-induced cascade reaction (Figure 43) is another approach to tertiary α-fluoro ketones. In contrary to the α-amino acid systems introduced in the last chapter, the deprotection of the benzyl ester **A** to the free acid **B** initiates the ultimate decarboxylation step to arrive at the desired α-fluoro ketone **D** *via* enolic species **C**.

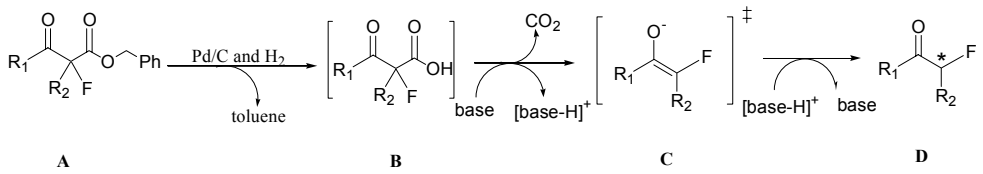


Figure 43: *The three steps of the Pd-induced cascade reaction*

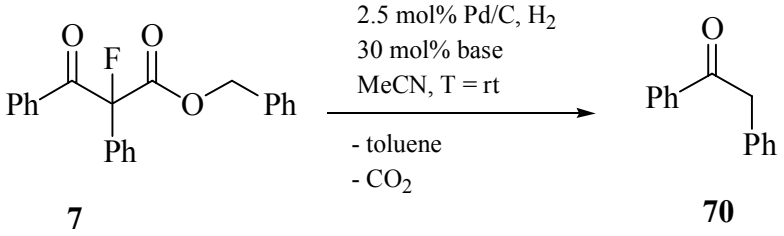
An advantage of the deprotection step is that the amount of substrate is propably kept low compared to the amount of chiral base. Furthermore, even sensitive ß-oxo acids **B** which are not stable as free acids can be applied in the protected form. However, heterogeneous catalytic systems may bear reproducibility problems and the supporting material plays an important role[98]. In the special case of this cascade reaction it was found that the kind of Palladium on charcoal has a strong influence on the enantiomeric excess[29].

4.3.1 General standard procedure

Employing the catalytic cascade reaction in order to obtain optically active fluoro ketones, the substrate (0.17 mmol) and the chiral base (30 mol%) were dissolved in MeCN (10 mL). Then the Pd catalyst (2.5 mol%) was added and the hydrogen atmosphere was provided with a gasbag. After the time indicated, the reaction mixture was filtered through 10 cm of Celite 545 (washed with CH_2Cl_2) in order to remove the Pd on charcoal. The solvents were evaporated at room temp. To remove the base, the residue was filtered through a small SiO_2 column with CH_2Cl_2.

4.3.2 The 2-fluoro-1,2-diphenylethanone system

Starting from the linear compound **7** in the first experiments with Pd/C type 5011 from Engelhard, full defluorination was observed with the achiral base 2-(methylamino)-ethanol) leading to deoxybenzoin **70** as product (Figure 44). This was unexpected as the C-F bond is usually stable towards hydrogenolysis with Pd catalysts, but the presence of a base and the benzylic position of the fluorine atom facilitate dehalogenation[99].



7 **70**

Figure 44: *Full defluorination of 2-fluoro-1,2-diphenylethanone*

4.3.3 Defluorination of α-fluoro ketones

Compared to other halogen compounds, fluorinated substances are the most stable ones, as the order of reactivity is RF << RCl < RBr < RI. Nevertheless, defluorination by hydrogenolysis is possible, depending on the position of fluorine in the molecule and on the conditions. Concerning the conditions, it generally can be said that the presence of a base in the reaction mixture and the use of a polar, hydroxylic solvent facilitate carbon-halogen cleavage[99].

In the special case of defluorination, the position of the fluorine is important. Allylic, vinylic, benzylic and aromatic fluorides are relatively easy to hydrogenolyse. A mechanism with participation of π bonds is proposed for that phenomenon[100]. The carbon-fluorine rupture requires 107–116 kcal/mol, the carbon–chloride bond dissociation energy is only 60–84 kcal/mol. While the hydrogenolysis of sp^3 carbon-fluorine bonds usually requires drastic conditions, it works at mild conditions (room temp., atmospheric hydrogen pressure) for allylic, vinylic, benzylic and aromatic fluorine atoms.

Defluorinations of compounds containing a fluorine in benzyl position, such as **7**, are known to literature[100]. However, they were carried out in the protic solvents methanol or ethanol. Therefore, the defluorination of **7** was not expected in the aprotic solvent acetonitrile. The proposed participation of the π system of the aromatic ring, which accounts for easy hydrogenolysis of benzylic fluorine, is illustrated for 1,1-difluoro-1,2-diphenylethane (Figure 45)[100].

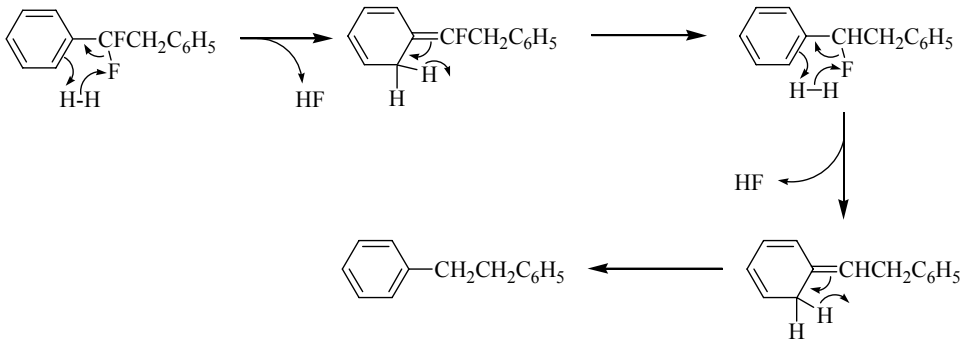


***Figure 45**: Defluorination of 1,1-difluoro-1,2-diphenylethane*

Reports on hydrogenolysis of fluorine in α-fluoro ketones are quite rare. In these cases, the π bond between carbon and oxygen participates in the cyclic mechanism[100]. When 2-fluoro-1-phenylethanone was hydrogenated in order to obtain 2-fluoro-1-phenylethanol, it appeared that this reaction only worked smooth if the starting material was carefully purified and there were no traces of acid (Figure 46)[101]. Otherwise, defluorination arriving at 1-phenylethanol took place. On the other hand, under the same conditions, no defluorination occurred with 1-phenyl-2-fluoroethanol as starting material.

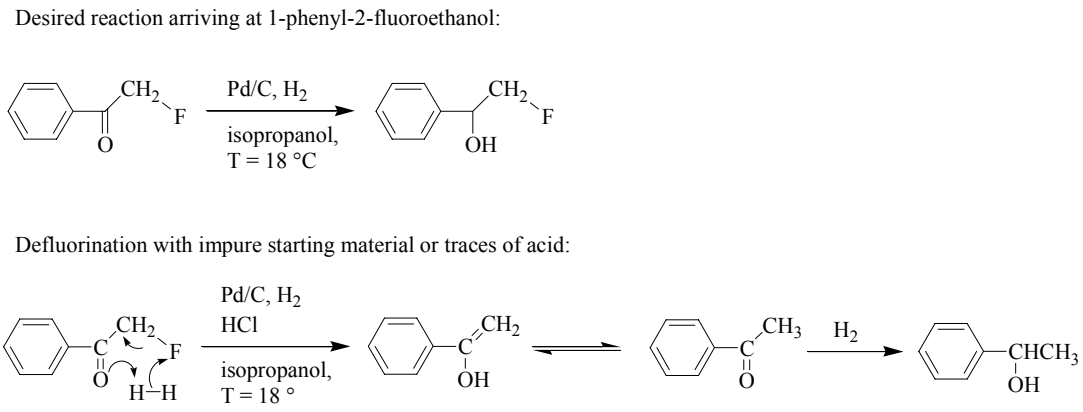
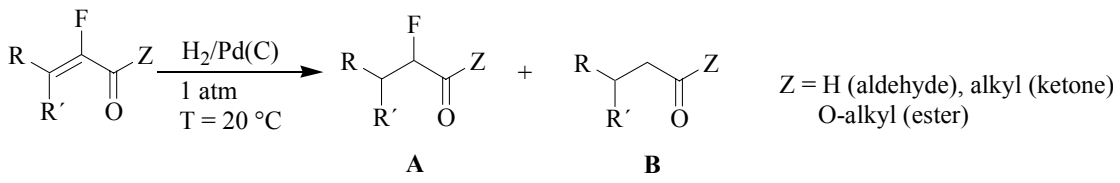


Figure 46: *Defluorination of 2-fluoro-1-phenyl-ethanone*

This example of an α-fluoro ketone affects our catalytic systems. Therefore, a partial dehalogenation cannot be excluded, although the solvent used is not the same (e.g., the reaction described above was slower in methanol). One last example should show that the α-fluoro ketone function will not inevitably promote defluorination. The catalytic hydrogenation of α,ß-unsaturated α-fluoro aldehydes, ketones and esters gave exclusively the α-fluoro ketones **A** in the case of an alkyl group for R and R´ (Figure 47)[102]. But in the case of a phenyl group for R or R´, the defluorinated byproduct **B** was found in 23-60% yield. This example is interesting as the substrate has a second



R and R´ = alkyl: exclusively compound **A**
R or R´= phenyl: up to 60% defluorinated compound **B**

Figure 47: *Hydrogenation of α,ß-unsaturated α-fluoro carbonyl compounds*

functionality, the vinyl system, which facilitates the cleavage of the C–F bond. However, it does not defluorinate except if there is a phenyl group in R or R´ position. Before HUDLICKY proposed a concerted mechanism to explain the readiness of the hydrogenolysis in allylic and vinylic fluorides[103,104], he stated something very suitable for the defluorination in an earlier review: "…it is very difficult to draw any conclusions as to whether a fluorine atom will stand the hydrogenation, or be replaced by hydrogen. The author´s impression is that in this respect fluorine behaves just in the opposite way one expects or desires"[105].

Another route which enables defluorination is photoreduction. For the cyclic α-fluoroketones 2-fluoro-cyclohexanone **10** and 2-fluoro-1-tetralone **12**, photochemical induced defluorination was reported[106,107].

4.3.4 The 2-fluorocyclohexanone system

With **9** another problem emerged, since the reaction product 2-fluorocyclohexanone **10** was too volatile for work-up. Furthermore, HPLC detection was another difficulty. Therefore, this system was not further pursued.

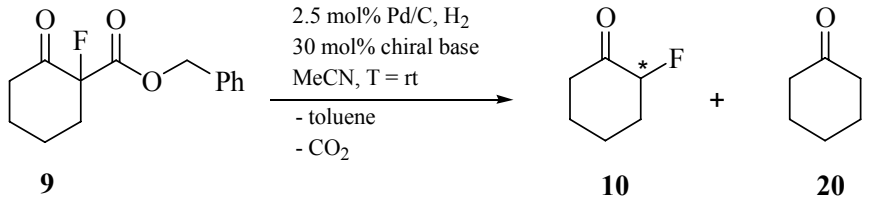


Figure 48: *The 2-fluoro-cyclohexanone system*

4.3.5 The 2-fluoro-1-tetralone system

Benzyl 2-fluoro-1-tetralone-2-carboxylate **11** was a suitable starting material for our studies. When submitted to the above conditions, the expected 2-fluoro-1-tetralone **12** was isolated besides small amounts of tetralone **23**, the defluorination product, and 2-fluoro-1-tetralol **27** coming from the overreduction of **12** (Figure 49). The relative quantities of each product and the ee of **12** are strongly dependent on the conditions.

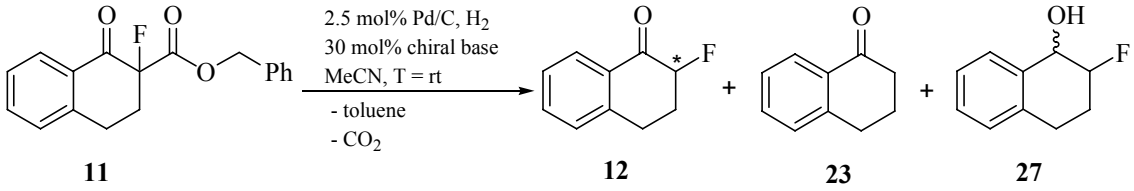


Figure 49: *Catalysis with benzyl 2-fluoro-1-tetralone-2-carboxylate **11***

4.3.5.1 Testing of different Pd catalysts

Especially the nature of the catalyst, palladium on charcoal, is crucial. The different surface properties and Pd and the H_2O content are sufficient to induce great differences in reactivity or enantioselectivity. For example, with the usually employed 5% Pd/C type Engelhard 5011[108] problems of reproducibility were observed (ee of **12** varied from

28 to 66%, in the presence of quinidine as a base, at the same time the yield of **23** was 0 to 30%). Therefore, other Pd/C catalysts were tested. Pd/C Engelhard 5067 was tried, first delivering good results (Table 1, entry 1), later again causing reproduction problems. For this reason, Pd/C Fluka 75992 and 75990 were tested (entries 2 and 3) with inferior results to Pd/C Merck 807104 (entry 4). This type brought constant and reproducible results, only in a few cases the ee dropped. With Pd(0) gained by $PdCl_2$ reduction, the reaction rate was low (entry 5). The cleavage of the benzyl ester can also be achieved by the Wilkinson catalyst using a silane as hydrogen source[109]. However the homogeneous catalysis conditions with elemental hydrogen resulted in a low reaction rate and the ee dropped dramatically (entry 6). Therefore, further catalyses were performed with Pd/C type 807104 from Merck.

Table 7: Influence of the supported catalyst. Conditions: MeCN, rt., 30 mol% quinine **52**, H_2 delivered by a gasbag, except entry 6 (40 bar).

Entry	Catalyst (mol%)	t [h]	Products		
			12 (%)	23(%)	ee of (*S*)-12 (%)
1	5%Pd/C Engelhard 5067[110] (2.5)	1	96; 94	4; 6	62.6; 56.9
2	5% Pd/C Fluka 75992[111] (2.5)	1	98; 99	2; 1	63.1; 59.9
3	10% Pd/C Fluka 75990[112] (2.5)	1	98; 92	2; 8	50.7; 65.6
4	10% Pd/C Merck 807104[113] (2.5)	1	95; 74	traces[a]	66.0; 67.9
5	Pd (0) (from $PdCl_2$) (25)	2	14; 17	traces	59.8; 51.2
6	$Rh(PPh_3)_3Cl$ (2.5)	2	2; 2	traces	20.5; 18.3

[a] traces: < 0.4 %

4.3.5.2 Testing of different chiral bases

Aminoalcohols like **65–67** led to good results in asymmetric protonation of tetralone enolic species[27,28,29] and they were tested first in our experiments (Table 8). However, bases **65–67** and aminoalcohols **68**, **69**, are ineffective with fluoro compound **11** (entries 1–5). Poor enantioselectivities of fluorotetralone **12** were observed and high amounts of tetralone **23** were found in most cases. Employing the natural cinchona alkaloids **28**, **51**, **49** and **52** to the catalysis, promising high stereoselectivities with up to 65% ee were obtained (entries 6–9). Besides, only little defluorination occurred with them.

Table 8: Variation of the chiral base. Conditions: Pd/C Merck 807104 (2.5 mol%), base (30 mol%), MeCN, rt., H_2 delivered by a gasbag.

Entry	Base [30 mol%]	t [h]	Products 12 (%)	23 (%)	27 (%)	ee of 12 (%) (config.)
1	(-)-ephedrine **65**	0.5	60; 74	40; 26	n.d.[b]	1.5; 1.7 (*R*)
2	(-)-norephedrine **66**	0.5	71; 71	29; 29	n.d.	0.6; 1.1 (*R*)
3	(+)-aminoborneol **67**	0.5	69; 73	31; 27	traces[a]	0
4	(-)-phenylglycinol **68**	0.5	52; 71	1; 5	n.d.; 1	3.4; 0.8 (*S*)
5	(+)-*tert*-leucinol **69**	0.5	40; 53	60; 46	n.d.; 1	0.6; 1.3 (*S*)
6	cinchonine **28**	2	97; 98	3; 3	traces; n.d.	51.4; 51.5 (*R*)
7	cinchonidine **51**	2	95; 97	5; 3	n.d.; 0	50.0; 50.1 (*S*)
8	quinidine **49**	2	99; 87	traces; 13	0 ; n.d.	64.7; 64.8 (*R*)
9	quinine **52**	2	94; 93	6; 7	n.d.; n.d	62.5; 64.4 (*S*).
10	H-AEC **29**	2	96; 95	2; 2	0; 0	20.4; 17.9 (*S*)
11	tosyl-AEC **43**	2	95; 94	1; 1	4; 5	24.1; 14.7 (*S*)
12	2,4-di-nitro-AEC **45**	2	86; 85	3; 2	0; 0	6.7; 1.5 (*S*)
13	Ph-ECA **30**	2	97; 93	3; 7	n.d.; n.d.	20.0; 25.1 (*S*)
14	2-MeO-Ph-ECA **32**	2	96; 97	2; 4	2 ; n.d.	2,7; 2.4 (*S*)
15	3-MeO-Ph-ECA **33**	2	98; 96	2; 1	n.d.; 3	17.4; 19.4 (*S*)
16	4-MeO-Ph-ECA **34**	2	98; 95	1; 1	2; 4	24.9; 20.7 (*S*)
17	3,5-di-tert-butyl-Ph-ECA **35**	2	95; 89	1; traces	4; 2	8.1; 8.0 (*S*)
18	PhNHCO-cinchonine **47**	2	97; 97	1; 1	2; 2	5.9; 1.7 (*S*)
19	ß-isocupreidine **50**	2	97; 96	2; 2	1; 2	20.9, 21.1 (*S*)

[a] traces: < 0.4%
[b] n.d.: not detected at $\lambda = 254$ nm.

As commercial cinchona alkaloids delivered fruitful results, different derivatives of their framework were tested with good catalytic performances in other decarboxylation systems[25]. Examination of the results (entries 10–19) shows that with these bases as inductors only little defluorination and overreduction occurred. However, no base was found superior to quinine. The exchange of the hydroxyl group at C-9 by an amino group resulted in a decreased enantiomeric excess of 19% (entry 10). Whatever the substitution at this amino group was, enantioselectivity reached not more than 25% (entries 11-17). The transformation of the *C*-9-hydroxyl function into carbamate **47** or ß-isocupreidine **50** gave also disappointing results (entries 18, 19).

4.3.6.3 Variations with quinine

As quinine **52** (Table 8, entry 9) delivered the best results, further variations were carried out with this base (Table 9). Switching to THF as solvent slightly decreased the ee from 65 to 60% (Table 9, entry 1). With EtOAc the enantiomeric excess increased in one case, but the result was not reproducible (entry 2). Furthermore, defluorination increased in both solvents. At 45 °C, the optical inductions are identical to standard conditions, but more defluorination was found (entry 3). At low conversion of the substrate (entry 4) as well as at prolonged reaction time of 16 h (entry 5), the ee of **12** remains about 65%. Under these conditions, compound **12** did not racemise. However, the amount of tetralone **23** increased until it became major (91%, entry 6). Only at this long reaction time, the ee of **12** dropped to 8%. At 40 bar in an autoclave, after 15 min the enantiomeric excess was similar to the standard catalysis (entry 7). Taking the tenfold amount of Pd/C, there was a high degree of defluorination and overreduction. The ee dropped to 25% (entry 8). With the threefold amount of quinine, results are similar to the standard catalysis (entry 9). It would seem logical to correlate the decreasing ee with the liberation of racemizing HF during the defluorination step (entries 6, 8), but this was not always the case (entries 1-5, 7, 9).

Table 9: Variation of catalysis parameters. Standard conditions: Pd/C Merck 807104 (2.5 mol%); 30 mol% quinine **52**; MeCN, rt., H_2 delivered by a gasbag, t = 2 h)

Entry	Change / Standard conditions	Products			
		12 (%)	**23 (%)**	**27 (%)**	**ee of (*S*)-12 (%)**
1	solvent: THF	81; 77	11; 23	8; n.d.[b]	59.0; 61.8
2	solvent: EtOAc	86; 97	14; 2	n.d.; 1	70.3; 59.2
3	T = 45 °C	60; 86	32; 14	8; n.d	65.9; 68.0
4	t = 0.25 h	4; 5	traces[a]	0 ; 0	64.4; 66.6
5	t = 16 h	53; 64	35; 36	12; n.d.	69.8; 51.8
6	t = 52 h	9	91	n.d.	8.2
7	H_2 Pressure = 40 bar t = 0.25 h	12; 16	traces	0; 0	64.1; 59.9
8	Pd / C, 25 mol%.	5; 3	57; 62	38; 35	24.6; 26.0
9	**52**, 90 mol%	98	2	n.d.	55.0

[a] traces: < 0.4%

[b] n.d.: not detected at λ = 254 nm.

4.3.6.4 Further testings

Further reactions have been carried out in order to get an idea how defluorination to **23** occurred (Table 10). Stirring enantioenriched **12** under catalysis standard conditions (Pd/C, quinine, MeCN, rt.), under hydrogen atmosphere the ee stayed constant, but 1-tetralone **23** and alcohol **27** were also forming (entry 1). In the same run without hydrogen and for a longer reaction time, the ee dropped but no byproduct was formed (entry 2). Analogous experiments were performed with racemic **12**. Under hydrogen atmosphere no enantiomeric excess was detected, but again byproducts **23** and **27** were found (entry 3), while no transformation was observed in the absence of hydrogen (entry 4). As expected, racemic **11** was stable under standard conditions in the abscence of hydrogen (entry 5). From these experiments, it appears that defluorination is probably a hydrogenolysis (compare runs 1 and 3) and that the liberated HF did not racemise **12**. On the contrary, the supported catalyst is racemising even without hydrogen (entry 2), probably due to the acidity of the α-H of the α-fluoro ketone.

Table 10: Further experiments (reaction conditions: Pd/C Merck 807104, 30 mol% quinine **52**)

Entry	**Substrate**	**H_2**	**t [h]**	**Products**			
				12 (%)	**23 (%)**	**27 (%)**	**ee of (*S*)-12 (%)**
1	**12** (50%; 55% ee)	yes	16	10; 68	74; 25	16; 6	50.6; 53.6
2	**12** (62.6%; 65.9% ee)	no	48	100; 100	0; 0	0 ; 0	23.0; 34.5
3	**12** (racemic)	yes	16	71; 94	27; 4	2; 2	racemic
4	**12** (racemic)	no	16	100; 100	0; 0	0; 0	racemic
5	**11** (racemic)	no	48	-	-	-	-

4.3.6 Analytics

Conversion was monitored with TLC (SiO_2) using PE:EtOAc (90:10) as eluent. Besides the byproduct 2-fluoro-1-tetralol **27**, all compounds were visible under UV. A quantification of the different substances was not possible in ^{1}H NMR if there were more compounds than 2-fluoro-1-tetralone **12** and tetralone **23** in the sample.

Therefore, quantitative HPLC performed with 2-methoxynaphthalene as internal standard. In order to obtain the calibration factors f_i, measurements with a calibration solution containing starting material **11** and all 3 possible products **12**, **23**, **27** were made. The calibration chromatogram is shown in Figure 50 (2-fluoro-1-tetralone with an ee of 65.3% ee). For the byproduct 2-fluoro-1-tetralol **27**, 4 peaks are visible for the 4 stereoisomers, at 25.8/28.4 min for the *cis*-isomers, 27.6/30.0 for the *trans*-isomers. The peaks at 27.6 min and 28.4 are not separated, as substance **27** only appeared in certain cases in higher amounts.

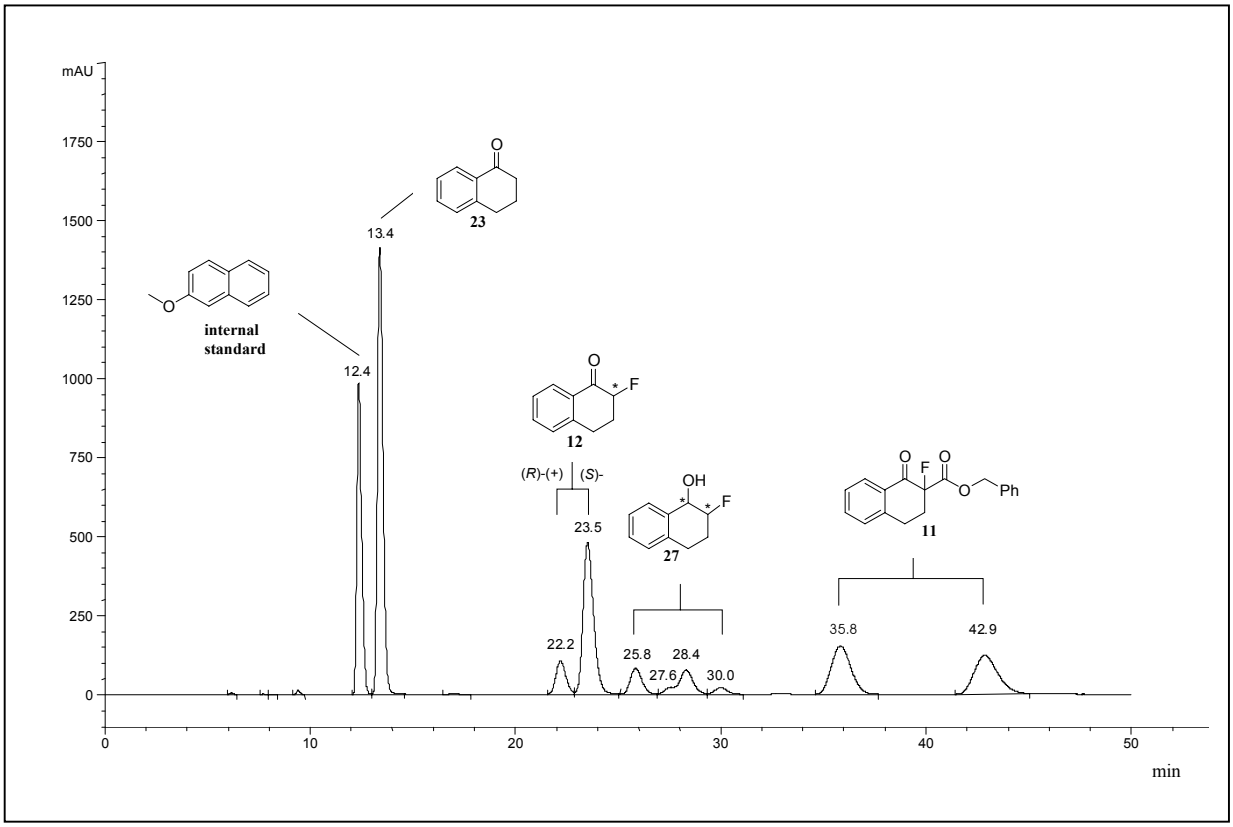


Figure 50: *HPLC-chromatogram*

The calibration factor f_i gives a relation between mass and peak area of internal standard and compound i (formula 1):

$$f_i = \frac{m_i \times A_{St}}{A_i \times m_{St}} \qquad (1) \qquad\qquad m_i = \frac{m_{St} \times f_i \times A_i}{A_{St}} \qquad (2)$$

i = compounds **11**, **12**, **23** and **27** A = integral area

st = standard (2-methoxynaphthalene) m = mass [mg]

Formula (2) follows from formula (1) and allows the calculation of the mass m_i and therefore of the yield.

First HPLC measurements were made at 254 nm detection wavelength. It appeared that 2-fluoro-1-tetralol **27**, which was not found in the ^{1}H NMR of the first catalytic runs, could not be detected at 254 nm. After assuring that the new byproduct was 2-fluoro-tetralol (synthesis by reduction of 2-fluoro-1-tetralone, analytics: mass, ^{1}H NMR, single injection HPLC), a suitable detection wavelength for all compounds was found with 210 nm.

The assignment optical rotation/configuration is based on an enantiomerically enriched sample of **12**[114].

5 Experimental Part

5.1 General

5.1.1 Working conditions

Bought chemicals were used without purification, liquids were distilled before use. The following reactions were carried out under nitrogen atmosphere, except the saponification of the malonates. The drying and nitrogen saturation of the solvents was carried out in circulation distils with the following dessicants:

- Dichloromethane: P_2O_5
- Ethanol: Mg
- Tetrahydrofuran: Na/K alloy
- Toluene: Na
- Triethylamine: CaH_2

For chromatography silica gel was used (ordinary: Merck 60, mesh 0.063–0.200 mm; flash: Merck 9385, 230–400 mesh), TLC monitoring was performed with aluminium plates from Merck with fluorescent indicator (SiO_2 60 F254, thickness of layer 0.2 mm).

Bulb-to-bulb distillations were carried out with a distillation apparatus type GKR-50 from Büchi company.

Vacuum designations correspond to following pressures:
Oil pump vacuum (OV): 1–2 Torr
High vacuum (HV): $<10^{-3}$ Torr

5.1.2 Analytics

Melting points

Büchi SMP 20

The melting points given are uncorrected.

IR spectra

Beckman Acculab 3

The intensities are given in the following way: s = strong, m = middle, w = weak, br = broad.

NMR spectroscopy

Bruker AC 250 (250 MHz), Avance 300 (300 MHz), Avance 400 (400 MHz) and Avance 600 (600 MHz).

The spectra were measured in deuterated solvents from Deutero company. The chemical shifts δ were given in ppm with tetramethylsilane as external standard. Coupling constants were indicated in Hz. Multiplicities were abbreviated as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. All spectra were analyzed according to first order.

Mass spectra

EI MS: Finnigan MAT 311 A, CI and FD MS: Finnigan MAT 95, GC CI MS: JOEL D-300.

The intensities are relative to the most intense signal. Only the most intense peak of a cluster is given.

Optical rotary power

Perkin Elmer Polarimeter 241

Measured at room temp. with a 1 dm cell.

Elemental analysis

Elementar Vario EL III

Gas chromatography

Hewlett Packard HP 5890 and Thermoquest 8130-10, integrator: Spectra Physics SP 4270. Injection amount 0.1 µL of a sample with a concentration of about 5 mg/mL in CH_2Cl_2. Precise conditions for the catalytic systems leading to amino acid derivatives are given in chapter 5.5.1.2.

HPLC

Apparatus: Hewlett Packard HP1090M, column thermostat: Agilent 1100 series, diode array detector measuring at 210 and 254 nm, column: Daicel OD-H (length 250 mm, 5 µm inner diameter), solvent mixture: hexane:isopropanol 97:3

Injection of 5 µL (3 mg/mL) at a flow of 0.6 mL/min resulting in a system pressure of about 45 bar. The retention times for the detected compounds are given in chapter 5.5.2.

5.2 Substrates for the α-amino acid system

5.2.1 Preparation of 2-*N*-acetylamino-2-ethoxycarbonylpropionic acid (1)

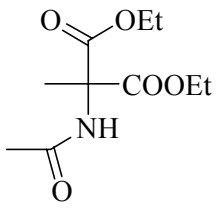
5.2.1.1 Diethyl 2-*N*-acetylamino-2-methylmalonate (14)[55]

Diethyl *N*-acetylaminomalonate (**13**) was added to a NaOEt solution (Na: 6.33 g, 275 mmol; 275 mL EtOH). After dissolution of **13**, methyl iodide (20.6 mL, 340 mmol) was added and the reaction mixture was refluxed for 20 h. The solvent was removed and the residue was dissolved in hot water. After cooling down, the formed crystals were collected and recrystallized from EtOH:PE (1:1).

$C_{10}H_{17}NO_5$ (231.3)

Yield: 43.9 g (190 mmol, 76%), colorless solid

Mp: 87–89 °C (lit. 88–90 °C)

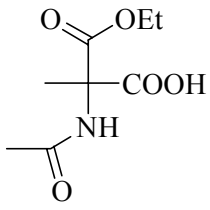


^{1}H NMR (250 MHz, $CDCl_3$): δ [ppm] = 1.25 (t, ^3J = 7.1 Hz, 6 H, CH_2CH_3), 1.75 (s, 3 H, CH_3), 2.02 (s, 3 H, $COCH_3$), 4.23 (q, ^3J = 7.1 Hz, 4 H, CH_2CH_3), 6.82 (s, 1 H, NH)

5.2.1.2 2-*N*-Acetylamino-2-ethoxycarbonylpropionic acid (1)[58]

To diethyl 2-*N*-acetylamino-2-methylmalonate (**14**) (10.0 g, 43.2 mmol) in ethanol (30 mL), an aqueous solution of KOH (2.92 g, 43.2 mmol in 2.6 mL water) was added dropwise. After stirring the reaction mixture for 5 d at room temp., the solvents were removed *in vacuo*. The aqueous solution of the residue was washed 3 × with EtOAc to remove the starting material from the product. The water phase was acidified with 2 N HCl at 0 °C. The precipitating product was extracted 3 × with EtOAc. The organic layers were dried over Na_2SO_4. After removal of the solvents, the crude product was recrystallised from EtOAc:hexane (2:1).

$C_8H_{13}NO_5$ (203.2)



Yield: 5.10 g (25.3 mmol, 58%), colorless solid

Mp: 142–143 °C (lit. 135–136 °C), (dec., $-CO_2$)

IR (KBr): ν [cm^{-1}] = 3320m (N–H); 2990w, 2940w (C–H); 2800–2200br (COOH); 1730s (C=O); 1600s (amide I); 1540s (amide II); 1450m, 1380w (C–H)

^{1}H NMR (250 MHz, [D_6]DMSO): δ [ppm] = 1.13 (t, ^3J = 7.0 Hz, 3 H, CH_2CH_3), 1.53 (s, 3 H, CH_3), 1.86 (s, 3 H, $COCH_3$), 4.08 (q, ^3J = 7.0 Hz, 2 H, CH_2CH_3), 8.15 (s, 1 H, NH), 13.46 (br s, 1 H, COOH)

MS (CI, NH_3): *m/z* (%) = 160.2 (92) [MH – CO_2], 177.2 (100) [M + NH_4 – COOH]

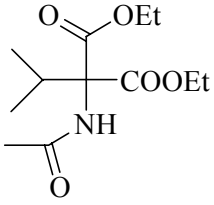
Elemental analysis:	calcd.:	C 47.29	H 6.45	N 6.89
	found:	C 47.34	H 6.49	N 6.82

5.2.2 Preparation of 2-*N*-acetylamino-2-ethoxycarbonyl-3-methylbutyric acid (2)

5.2.2.1 Diethyl 2-*N*-acetylamino-2-isopropylmalonate (15)[56]

Diethyl *N*-acetylaminomalonate (**13**) (15.0 g, 69.1 mmol) was added to a NaOEt solution (NaOEt: 5.17 g, 76.0 mmol; 125 mL EtOH). After dissolution of **13**, isopropyl iodide (6.9 mL, 69.1 mmol) was added and the reaction mixture was refluxed for 48 h. After removal of the solvent, the residue was dissolved in hot water. After cooling down, the formed crystals were collected and washed with PE.

$C_{12}H_{21}NO_5$ (259.3)



Yield: 3.62 g (14.0 mmol, 20%), colorless solid

Mp: 71–72 °C (lit. 73 °C)

^{1}H NMR (250 MHz, $CDCl_3$): δ [ppm] = 0.93 (d, ^3J = 6.9 Hz, 6 H, $CH(CH_3)_2$), 1.25 (t, ^3J = 7.1 Hz, 6 H, CH_2CH_3), 3.55 (s, 3 H, $COCH_3$), 2.75 (sept, ^3J = 6.9 Hz, 1 H, $CH(CH_3)_2$), 4.23 (q, ^3J = 7.1 Hz, 4 H, CH_2CH_3), 6.54 (s, 1 H, NH)

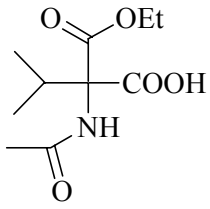
5.2.2.2 2-*N*-Acetylamino-2-ethoxycarbonyl-3-methylbutyric acid (2)

Diethyl 2-*N*-acetylamino-2-isopropyl-malonate (**15**) (4.96 g, 19.1 mmol) was dissolved in EtOH (10 mL). A solution of KOH (1.28 g, 19.4 mmol) in water (1.3 mL) and EtOH (5.2 mL) was added dropwise. After stirring for 48 h, the solvents were removed *in vacuo* at room temp. The aqueous solution of the residue was washed 3 × with EtOAc to remove the starting material from the product. The water phase was acidified with half-concentrated HCl at 0 °C. The precipitating product was extracted 3 × with EtOAc. The organic layers were dried over Na_2SO_4 adding charcoal to remove a pink color. Evaporation of the organic solvent yielded **2** as a colorless solid.

$C_{10}H_{17}NO_5$ (231.3)

Yield: 1.50 g (6.49 mmol, 34%), colorless solid

Mp: 130–132 °C (dec., $–CO_2$)



IR (KBr): ν [cm^{-1}] = 3360s (N–H), 2980w, 2950w, 2890w (C–H); 2700–2180br (COOH); 1780s, 1720s (C=O); 1615s (amide I), 1550s (amide II); 1470w, 1450w, 1420w (C–H)

^{1}H NMR (250 MHz, [D_6]DMSO): δ [ppm] = 0.84, 0.87 (2 d, ^3J = 6.9 Hz, 6 H, $CH(CH_3)_2$), 1.11 (t, ^3J = 7.1 Hz, 3 H, CH_2CH_3), 1.89 (s, 3 H, $COCH_3$), 2.40–2.57 (m, 1 H, $CH(CH_3)_2$), 3.93–4.17 (m, 2 H, CH_2CH_3), 7.94 (s, 1 H, NH), 13.27 (br s, 1 H, COOH)

MS (CI, NH_3): *m/z* (%) = 142.0 (7) [M – COOH – EtOH], 188.1 (100) [M – COOH], 205.1 (41) [M + NH_4 – COOH]

Elemental analysis:	calcd.:	C 51.94	H 7.41	N 6.06
	found:	C 52.10	H 7.25	N 6.20

5.2.3 Preparation of 2-*N*-acetylamino-2-ethoxycarbonyl-3-phenyl-propionic acid (3)

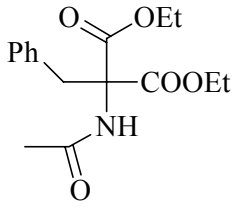
5.2.3.1 Diethyl 2-*N*-acetylamino-2-benzylmalonate (16)[57]

Diethyl acetylaminomalonate (**13**) (21.8 g, 100 mmol) was added to a NaOEt solution (NaOEt: 7.52 g, 110 mmol; 200 mL EtOH). After dissolution of **13,** benzyl chloride (11.6 mL, 100 mmol) was added and the reaction mixture was refluxed for 10 h. After removal of the solvent, the residue was dissolved in hot Et_2O and precipitated with PE (–30 °C).

$C_{16}H_{21}NO_5$ (307.3)

Yield: 12.9 g (42.0 mmol, 42%), colorless solid

Mp: 103–105 °C (lit. 104–106 °C)

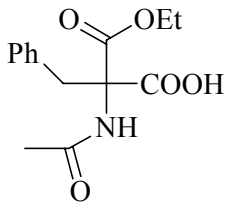


^{1}H NMR (250 MHz, $CDCl_3$): δ [ppm] = 1.30 (t, ^3J = 7.1 Hz, 6 H, CH_2CH_3), 2.03 (s, 3 H, $COCH_3$), 3.65 (s, 2 H, benzyl H), 4.27 (q, ^3J = 7.1 Hz, 4 H, CH_2CH_3), 6.52 (br s, 1 H, NH), 6.95–7.06 (m, 1 H, Ph), 7.20–7.28 (m, 4 H, Ph)

5.2.3.2 2-*N*-Acetylamino-2-ethoxycarbonyl-3-phenylpropionic acid (3)[59]

To a cooled (0 °C) suspension of diethyl 2-*N*-acetylamino-2-benzylmalonate (**16**) (12.5 g, 40.7 mmol) in EtOH (60 mL) an aqueous KOH solution (2.69 g, 40.7 mmol in 15 mL water) was added dropwise. After 2 d stirring, the solvents were removed *in vacuo* and the residue was taken up in EtOAc/H_2O. The aqueous phase was extracted 3 × with EtOAc in order to remove starting material. Then it was acidified at 0 °C with half-concentrated HCl. The precipitating product was extracted 3 × with EtOAc, the organic layers dried over Na_2SO_4 and the solvent was evaporated. After dissolving the crude product in hot $CDCl_3$, it was precipitated with PE (–30 °C).

$C_{14}H_{17}NO_5$ (279.3)



Yield: 4.40 g (15.8 mmol, 39%), colorless solid

Mp: 148–150 °C (lit. 129–130 °C), (dec., $-CO_2$)

IR (KBr): ν [cm^{-1}] = 3340s (N–H); 3020w, 2980w, 2940w (C–H); 2940–2100br (COOH); 1730s (C=O); 1610s (amide I); 1530s (amide II); 1450w, 1380w (C-H)

^{1}H NMR (250 MHz, [D_6]DMSO): δ [ppm] = 1.15 (t, ^3J = 7.1 Hz, 3 H, CH_2CH_3), 1.92 (s, 3 H, $COCH_3$), 3.37, 3.46 (2 d, ^2J = 13.6 Hz, 2 H, benzyl H), 4.11 (q, ^3J = 7.1 Hz, 2 H, CH_2CH_3), 6.94–7.03 (m, 2 H, Ph), 7.17–7.30 (m, 3 H, Ph), 7.83 (br s, 1 H, NH), 13.76 (br s, 1 H, COOH)

MS (CI, NH_3): *m/z* (%) = 188.1 (28) [M – COOH – EtOH], 206.2 (21) [M – COOH – C_2H_4], 234.2 (100) [M – COOH]

Elemental analysis:	calcd.:	C 60.21	H 6.14	N 5.02
	found:	C 59.61	H 6.03	N 4.92

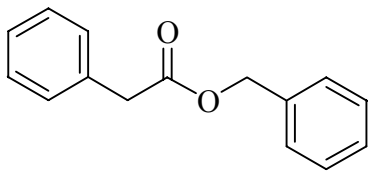
5.3 Substrates for the α-fluoro ketone system

5.3.1 Benzyl 2-fluoro-3-oxo-2,3-diphenylpropionate (7)

5.3.1.1 Benzyl phenylacetate (18)[30]

Phenylacetic acid (19.9 g, 146 mmol), benzyl bromide (27.5 g, 161 mmol) and K_2CO_3 (24.2 g, 175 mmol) were refluxed in acetone (300 mL) for 11 h. The cold reaction mixture was filtered in order to remove the K_2CO_3. Water was added and after 3 × extraction with Et_2O, the combined organic layers were washed with saturated NaCl solution. After drying over $MgSO_4$ and evaporation, the crude product was flash chromatographed on SiO_2 (PE:EtOAc 95:5).

$C_{15}H_{14}O_2$ (226.3)
Yield: 22.3 g (98.6 mmol, 68%),
colorless liquid



^{1}H NMR (250 MHz, $CDCl_3$): δ [ppm] = 3.70 (s, 2 H, PhC*H*$_2$CO), 5.14 (s, 2 H; PhC*H*$_2$OCO), 7.28–7.50 (m, 10 H, Ph)

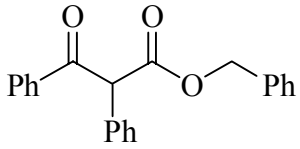
5.3.1.2 Benzyl 3-oxo-2,3-diphenylpropionate (19)[30]

To HMDS (5.1 mL, 24 mmol) diluted with THF (15 mL), BuLi (1.6 M solution, 15 mL, 24 mmol) was added dropwise at –78 °C. The mixture was stirred for 45 minutes at this temperature, then benzyl phenylacetate (**18**) (3.40 g, 15 mmol) in THF (15 mL) was added dropwise. After 15 min, the cooling was removed and the batch was stirred for 2 h at room temp. Benzoyl chloride (2.3 mL; 18 mmol) was added dropwise at –78 °C and the mixture was stirred for 2 h. The reaction mixture was poured into 2 M HCl (containing ice-pieces) and extracted 3 × with Et_2O. The organic layers were washed with saturated NaCl solution, dried over $MgSO_4$, filtered and evaporated. The crude product was chromatographed on SiO_2 (PE:EtOAc 95:5). The orange oil was taken up in Et_2O, precipitated with PE and stored at –30 °C.

$C_{22}H_{18}O_3$ (330.4)

Yield: 2.20 g (6.66 mmol, 44%), colorless solid

Mp: 64–67 °C (Lit. 63 °C)



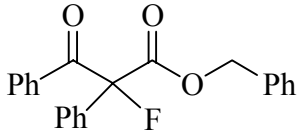
^{1}H NMR (250 MHz, $CDCl_3$): δ [ppm] = 5.13 (s, 2 H, benzyl H), 5.58 (s, 1 H, Ph), 7.15–7.38 (m, 11 H, Ph), 7.39–7.49 (m, 1 H, Ph), 7.81–7.90 (m, 2 H, Ph)

5.3.1.3 Benzyl 2-fluoro-3-oxo-2,3-diphenylpropionate (7)

To a suspension of NaH (60% in mineral oil; 120 mg; 3.00 mmol) in THF (10 mL), benzyl 3-oxo-2,3-diphenyl-propionate (**19**) (990 mg, 3.00 mmol) in THF (20 mL) was added slowly at 0 °C. The mixture was stirred for 0.5 h at 0 °C and then 1 h at room temp. It was diluted with DMF (30 mL) and Selectfluor™ (1.06 g, 3.00 mmol) was added in one portion. The reaction mixture was stirred overnight at room temp. After addition of water it was extracted 3 × with Et_2O, dried over $MgSO_4$ and evaporated. The crude product was flash chromatographed on SiO_2 (PE:EtOAc 95:5) and also on ordinary SiO_2 (CH_2Cl_2). However, a trace of the byproduct fluorinated at the benzyl position (about 3%) could not be removed.

$C_{22}H_{17}FO_3$ (348.4)

Yield: 570 mg (1.64 mmol, 55%), colorless oil



^{1}H NMR (250 MHz, $CDCl_3$): δ [ppm] = 5.33, 5.38 (2 d, ^2J = 10.0 Hz, 1 H, benzyl H), 7.28–7.67 (m, 13 H, Ph), 7.92–7.99 (m, 2 H, Ph)
byproduct: δ [ppm] = 5.85 (d, $^2J_{H,F}$ = 48 Hz, 0.03 H, benzyl F)

^{13}C DEPT135 NMR ($CDCl_3$, 62.9 MHz): δ [ppm] = 68.7 (s, CH_2), 126.1 (d, J = 8.8 ppm Hz, CH), 128.6 (s, CH), 129.0 (s, CH), 129.8 (s, CH), 130.6 (d, J = 5.0 Hz, CH), 134.3 (s, CH)

^{19}F NMR (235 MHz, $CDCl_3$): δ [ppm] = – 157.2 (s)
byproduct: δ [ppm] = –179.87 (d, $^2J_{H,F}$ = 47 Hz, benzyl F)

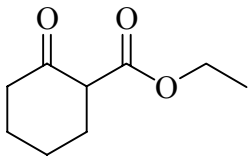
GC–MS (CI, NH_3): 6.82 min, *m/z* (%) = 244 (36) [M – PhCO], 262 (100) [M – PhCO + NH_4]; byproduct: 7.07 min, *m/z* (%) = 134 (22) [$PhCH_2COO$], 220 (11) [PhCOCHPhCOO], 268 (100)

5.3.2 Benzyl 2-fluorocyclohexanone-2-carboxylate (9)

5.3.2.1 Ethyl cyclohexanone-2-carboxylate (21)[60]

Cyclohexanone (35.9 mL, 338 mmol) in THF (60 mL) was added to a suspension of NaH (16.6 g, 690 mmol) in THF (300 mL). After stirring for 45 min at room temp., diethyl carbonate (209 mL, 1.73 mol) was added dropwise. The reaction mixture was stirred for 1 h at room temp., then refluxed for 4 h at 70 °C. The cold batch was hydrolysed with 3 M acetic acid (350 mL) and extracted three times with Et_2O. The combined organic layers were washed with $NaHCO_3$ and saturated NaCl solution and dried over $MgSO_4$. After removal of the solvent, purification was performed by fractionated destillation, first removing the lower boiling diethyl carbonate at 25 – 60 °C (2 Torr).

$C_9H_{14}O_3$ (170.2)
Yield: 19.7 g (116 mmol, 52%), colorless liquid
Bp: 70–80 °C (1 Torr)



^{1}H NMR (250 MHz, $CDCl_3$): δ [ppm] = 1.28, 1.29 (t enol, t ketone , ^3J = 7.1 Hz, 3 H, CH_2CH_3), 1.49–2.01 (m, 4 H, CH_2), 2.06–2.54 (m, 4 H, CH_2), 3.26–3.50 (m, 0.2 H, H ketone), 4.19, 4.20 (q enol, q ketone, ^3J = 7.1 Hz, 2 H, CH_2CH_3), 12.19 (s, 0.8 H, OH enol)

5.3.2.2 Benzyl cyclohexanone-2-carboxylate (22)

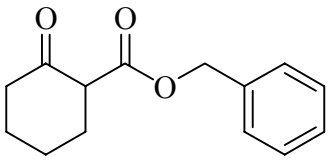
A mixture of ethyl cyclohexanone-2-carboxylate (**21**) (15.0 g, 88.1 mmol), benzyl alcohol (45.8 mL, 441 mmol) and toluene (500 mL) was stirred for 9 d at 120 °C.

Ethanol and toluene were removed at 150 °C without vacuum, then the benzyl alcohol at 130 °C (1 Torr). The product was purified by distillation in high vacuum ($3 \cdot 10^{-2}$ Torr).

$C_{14}H_{16}O_3$ (232.3)

Yield: 12.8 g (55.1 mmol, 63%), colorless liquid

Bp: 100–110 °C ($3 \cdot 10^{-2}$ Torr)



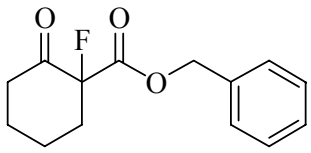
^{1}H NMR (250 MHz, $CDCl_3$): δ [ppm] = 1.47–2.00 (m, 4 H, CH_2), 2.10–2.59 (m, 4 H, CH_2), 3.39–3.49 (m, 0.2 H, H ketone), 5.17, 5.26 (2 d, ^2J = 12.5 Hz, 2 H, benzyl H), 7.27–7.48 (m, 5 H, Ph), 12.16 (s, 0.8 H, OH enol)

5.3.2.3 Benzyl 2-fluorocyclohexanone-2-carboxylate (9)

To benzyl cyclohexanone-2-carboxylate (**22**) (1.50 g, 6.46 mmol) in acetonitrile (65 mL), Selectfluor™ (2.29 g, 6.46 mmol) was added in one portion and the reaction mixture was stirred for 20 h. After removal of the solvent, the residue was taken up in CH_2Cl_2/H_2O and extracted 3 × with CH_2Cl_2. The organic layer was washed with water and dried over $MgSO_4$, filtered and evaporated. The crude product was chromatographed on SiO_2 (PE:EtOAc 90:10).

$C_{14}H_{15}FO_3$ (250.3)

Yield: 1.30 g (5.19 mmol, 80%), colorless liquid



IR (neat): ν [cm^{-1}] = 3080w, 3060w, 2980m, 2890w (C–H); 1790s, 1760s (C=O); 1540w, 1490m (C=C); 1370w, 1420w (C–H)

^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm] = 1.74–1.98 (m, 4 H, CH_2), 2.08–2.24 (m, 1 H, CH_2), 2.36–2.63 (m, 2 H, CH_2), 2.65–2.79 (m, 1 H, CH_2), 5.24, 5.29 (d, ^2J = 12.1 Hz, 2 H, benzyl H), 7.30–7.42 (m, 5H, Ph)

^{13}C NMR (75.5 MHz, $CDCl_3$): δ [ppm] = 20.8 (d, J = 5.2 Hz), 26.6 (s), 36.0 (d, J = 21.4 Hz), 39.6 (s), 67.8 (s), 96.4 (d, J = 196.8 Hz, *C*F), 128.3 (s), 128.6 (s), 128.7 (s), 134.8 (s), 166.8 (d, J = 25.1 Hz, *C*=O ester), 201.8 (d, J = 19.9 Hz, *C*=O oxo)

^{19}F NMR (235 MHz, $CDCl_3$): δ [ppm] = 160.97 (ddd, $^3J_{H,F\,(aa)}$ = 21.9, $^3J_{H,F\,(ae)}$ = 13.7, ^4J = 5.1 Hz)

GC–MS (CI, NH_3): *m/z* (%) = 108 (29) [$PhCH_2OH$], 134 (5) [$C_6H_9FO + NH_4$], 250 (4) [M], 268 (100) [$M + NH_4$]

5.3.3 Benzyl 2-fluoro-1-tetralone-2-carboxylate (11)

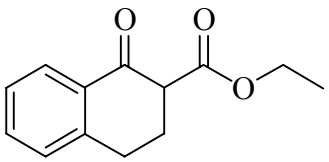
5.3.3.1 Ethyl 1-tetralone-2-carboxylate (24)[23]

To a suspension of NaH (5.23 g, 218 mmol) in toluene (70 mL), diethyl carbonate (73 mL, 602 mmol) was added. A solution of 1-tetralone (16.0 g, 111 mmol) in toluene (250 mL) was added dropwise. The reaction mixture was stirred for 2 h at room temp. Refluxing the brown suspension for 10 h afforded a yellow/brown solid which was dissolved in ice water containing ethanol (10 mL). After dropwise acidification with 2 M HCl, the aqueous phase was extracted 3 × with Et_2O. The combined organic layers were dried over $MgSO_4$ and the solvents and diethyl carbonate were evaporated. The crude product was purified by distillation ($1 \cdot 10^{-3}$ Torr, T = 200 °C).

$C_{18}H_{16}O_3$ (218.3)

Yield: 16.1 g (73.8 mmol, 67%), yellow liquid

Bp: 200 °C ($1 \cdot 10^{-3}$ Torr)



^{1}H NMR (250 MHz, $CDCl_3$): δ [ppm] = 1.32 (t ketone, t enol, ^3J = 7.2 Hz, 3 H, CH_2CH_3), 2.25–2.40 (m, 0.6 H, CH_2 ketone), 2.49–2.63 (m, 1.4 H, CH_2 enol), 2.72–2.87 (m, 1.4 H, CH_2 enol), 2.95–3.10 (m, 0.6 H, CH_2 ketone), 3.60 (dd, $^3J_{(aa)}$ = 10.3 Hz, $^3J_{(ae)}$ = 4.8 Hz, 0.3 H ketone), 4.25, 4.28 (q ketone, q enol, ^3J = 7.2 Hz, 2 H, CH_2CH_3), 7.12–7.20 (m, 0.7 H, CH_2 enol), 7.20–7.39 (m, 2 H, Ph), 7.49 (td, ^3J = 7.4 Hz, ^4J = 1.4

Hz, 0.3 H, Ph ketone), 7.80 (dd, ^{3}J = 7.1 Hz, ^{4}J = 1.7 Hz, 0.7 H, Ph enol), 8.00 (dd, ^{3}J = 8.1 Hz, ^{4}J = 0.8 Hz, 0.3 H, Ph ketone), 12.2 (s, 0.7 H, OH enol)

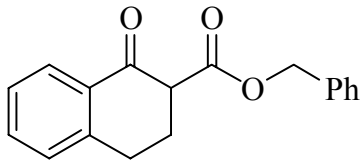
5.3.3.2 Benzyl 1-tetralone-2-carboxylate (25)

Ethyl 1-tetralone-2-carboxylate (**24**) (10.5 g, 48.1 mmol), benzyl alcohol (25 mL, 241 mmol) and toluene (250 mL) were stirred at 120 °C for 6 d. Toluene was removed at 150 °C. Afterwards the benzyl alcohol was distilled off at 150 °C (1 Torr). Purification with bulb-to-bulb distillation (170–210 °C, $1 \cdot 10^{-4}$ Torr).

$C_{18}H_{16}O_3$ (280.3)

Yield: 8 g (28.5 mmol, 59%), yellow liquid

Bp: 170–210 °C ($1 \cdot 10^{-4}$ Torr)



^{1}H NMR (250 MHz, $CDCl_3$): δ [ppm] = 2.32–2.73 (m, 2 H, CH_2), 2.78–2.87 (m, 1 H, CH_2), 2.95–3.10 (m, 1 H, CH_2), 3.70 (dd, $^{3}J_{(aa)}$ = 10.4 Hz, $^{3}J_{(ae)}$ = 4.7 Hz, 0.4 H, H ketone), 5.17, 5.26 (2 d, ^{2}J = 12.2 Hz, 2 H, benzyl H),), 7.12–7.54 (m, 8 H, Ph), 7.85 (dd, J = 7.3 Hz, J = 1.5 Hz, 0.6 H, Ph enol), 8.10 (d, J = 7.9 Hz, 0.4 H, Ph ketone), 12.45 (s, 0.6H, OH enol)

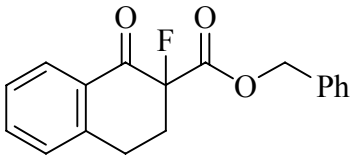
5.3.3.3 Benzyl 2-fluoro-1-tetralone-2-carboxylate (11)

To benzyl 1-tetralone-2-carboxylate (**25**) (2.34 g, 8.35 mmol) in acetonitrile (100 mL), Selectfluor™ (2.96 g, 8.35 mmol) was added in one portion. The reaction mixture was stirred for 19 h at room temp. After evaporation of the solvent, the remaining residue was taken up in H_2O/CH_2Cl_2 and extracted 3 × with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and evaporated. Chromatography on SiO_2 (PE:EtOAc 90:10) afforded an orange oil. Recrystallisation from Et_2O gave a colorless solid.

$C_{18}H_{15}FO_3$ (298.3)

Yield: 1.72 g (5.77 mmol, 69%), colorless needles

Mp: 64–65 °C



IR (KBr): ν [cm^{-1}] = 3500w, 3370w; 3060w, 3030w, 2940w, 2890w (C–H); 1760s, 1700s (C=O); 1600m, 1500w (C=C); 1490w, 1460m, 1430w (C–H)

^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm] = 2.55 (dddd, ^{3}J = 13.8 Hz, ^{3}J = 11.3 Hz, ^{3}J = 8.0 Hz, ^{4}J = 5.2 Hz, 1 H, CH_2), 2.72 (dddd, ^{3}J = 13.8 Hz, ^{3}J = 11.3 Hz, ^{3}J = 8.0 Hz, ^{4}J = 5.2 Hz, 1 H, CH_2), 3.00 (ddd, $^{3}J_{H,F(aa)}$ = 17.2 Hz, $^{3}J_{H,F(ae)}$ = 7.8 Hz, ^{3}J = 5.0 Hz, 1 H, CH_2), 3.17 (td, $^{3}J_{H,F(aa)}$ = 17.3 Hz, ^{3}J = 6.2 Hz, 1 H, CH_2), 5.22, 5.30 (2 d, ^{2}J = 12.3 Hz, 2 H, benzyl H), 7.22–7.33 (m, 6 H, Ph), 7.37 (t, ^{3}J = 8.1 Hz, 2 H, Ph), 7.55 (td, ^{3}J = 7.5 Hz, ^{4}J = 1.4 Hz, 1 H, Ph), 8.08 (dd, ^{3}J = 7.8 Hz, ^{4}J = 1.2 Hz, 1 H, Ph)

^{13}C NMR (75.5 MHz, $CDCl_3$): δ [ppm] = 24.8 (d, J = 7.3 Hz, CH_2); 31.9 (d, J = 22.1 Hz, CH_2), 67.7 (s, CH_2), 93.3 (d, J = 193.9 Hz, CF), 127.3 (s, CH), 128.0 (s, CH), 128.5 (d, J = 2.9 Hz, CH), 128.6 (s, CH), 128.8 (s, CH), 134.6 (s, CH), 132.7 (d, J = 193.9 Hz, C quart.), 143.1 (s, 2 C quart.), 167.2 (d, J = 26.5 Hz, C=O ester), 188.5 (d, J = 19.2 Hz, C=O oxo)

^{19}F NMR (235 MHz, $CDCl_3$): δ = – 164.94 (dd, $^{3}J_{H,F\,(aa)}$ = 22.4 Hz, $^{3}J_{H,F\,(ae)}$ = 10.3 Hz)

MS (EI, 70 eV): *m/z* (%) = 91 (100) [$PhCH_2$], 164 (43) [$C_{10}H_9FO$], 298.1 (27) [M]

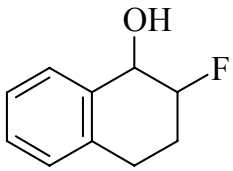
Elemental analysis:	calcd.:	C 72.47	H 5.07
	found:	C 72.21	H 4.84

5.3.4 2-Fluoro-1-tetralol (27)

To $NaBH_4$ (32.0 mg, 0.85 mmol) in isopropanol (10 mL), 2-fluoro-1-tetralone[115] (**12**) (320 mg, 1.95 mmol) in isopropanol (10 mL) was added dropwise at room temp. After stirring overnight, the reaction mixture was cooled and diluted HCl was added dropwise until no more hydrogen developed. The solvents were removed, the residue was taken up in H_2O/CH_2Cl_2 and extracted with CH_2Cl_2 (3 × 25 mL). After removal of the solvents, the residue was chromatographed on SiO_2 (CH_2Cl_2), yielding a colorless oil (170 mg, 1.02 mmol).

$C_{10}H_{11}FO$ (166.2)

Yield: 170 mg (1.02 mmol, 53%),
Colorless oil



^{1}H NMR (600 MHz, $CDCl_3$): δ [ppm] = 1.98–2.13 (m, 1 H, CH_2), 2.22–2.31 (m, 0.3 H, CH_2), 2.36–2.50 (m, 1.3 H, CH_2, OH), 2.79–2.85 (m, 0.7 H, CH_2), 2.88–3.01 (m, 0.7 H, CH_2), 3.02–3.10 (m, 1 H, CH_2), 4.79 (ddddd, $^2J_{H,F}$ = 50.2 Hz, $^3J_{(aa/ee)}$ = 9.7 Hz, $^3J_{(aa/ee)}$ = 6.7 Hz, ^4J = 3.5 Hz, ^5J = 0.4 Hz, 0.3 H, *trans*-isomer), 4.80–4.89 (m, 1H, CH), 5.01 (ddddd, $^2J_{H,F}$ = 49.7 Hz, $^3J_{(aa/ee)}$ = 8.6 Hz, $^3J_{(ae)}$ = 3.4 Hz, ^4J = 2.7 Hz, ^5J = 0.4, 0.7 H, FCH *cis*-isomer), 7.12–7.17 (m, 1 H, Ph), 7.23–7.30 (m, 2 H, Ph), 7.52–7.55 (m, 0.7 H, Ph, *cis*-isomer), 7.55–7.58 (m, 0.3 H, Ph, *trans*-isomer)

MS (EI, 70 eV): *m/z* (%) = 91 (36), 119 (100), 148 (70) [M – H_2O], 166 (42) [M]

5.4 Synthesis of the catalysts

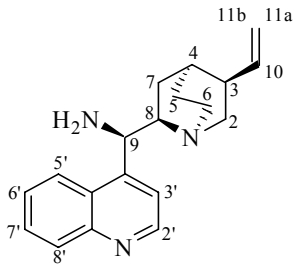
5.4.1 9-Amino(9-deoxy)epicinchonine (29)[51]

To a cooled (0 °C) suspension of cinchonine (25.0 g, 84.9 mmol) in THF (400 mL), 106 mL of a benzene solution of HN_3[116] (102 mmol, c = 0.96 mol/l) and PPh_3 (26.8 g, 102 mmol) were added. After stirring for 5 min, diisopropylazodicarboxylate (18.3 mL, 93.4 mmol) in THF (80 mL) was added dropwise. After strirring 3 h at room temp., PPh_3 (22.3 g, 84.8 mmol) in THF (80 mL) was added and the reaction mixture was heated to 40 °C and stirred for another 3 h at this temperature. Then water (8.5 mL) was added and stirring was continued for further 3 h. The solvents were removed *in vacuo* and the residue was dissolved in 2 M HCl (400 mL). The aqueous phase was extracted 3 × with CH_2Cl_2. After removal of the solvents the crude hydrochloride was recrystallized from methanol. The hydrochloride (20.5 g, 50.8 mmol, 60%) was dissolved in water, neutralized with saturated Na_2CO_3 and extracted 3 × with CH_2Cl_2 to liberate the free base. After drying the organic layers over Na_2CO_3 and removal of the solvent, the yellow oil was purified by bulb-to-bulb distillation (220 °C/ 0.01 Torr).

$C_{19}H_{23}N_3$ (293.4)

Yield: 10.4 g (35.4 mmol, 42%), yellow oil

Bp: 220 °C (0.01 Torr)



IR (neat): ν [cm^{-1}] = 3380m, 3300w (N–H); 3080m, 3040w, 2940s, 2860s (C–H); 1640m, 1590s, 1570s, 1510s (C=C)

^{1}H NMR (250 MHz, $CDCl_3$): δ [ppm] = 0.85–1.00 (m, 1 H, H7b), 1.08–1.25 (m, 1 H, H7a), 1.51–1.60 (m, 3 H, H4, H5), 1.97 (s, 2 H, NH_2), 2.28 (m, 1 H, H3), 2.89–3.09 (m, 5 H, H2, H6, H8), 4.77 (d, ^3J = 9.9 Hz, 1 H, H9), 5.03–5.11 (m, 2 H, H11a, H11b), 5.87 (ddd, ^3J = 16.3 Hz, ^3J = 11.5 Hz, ^3J = 6.7 Hz, 1 H, H10), 7.56–7.63 (m, 2 H, H3', H7'), 7.68–7.76 (m, 1 H, H6'), 8.14 (d, ^3J = 8.3 Hz, 1 H, H5'), 8.36 (d, ^3J = 8.3 Hz, 1 H, H8'), 8.90 (d, ^3J = 4.4 Hz, 1 H, H2')

MS (EI, 70 eV): *m/z* (%) = 81.9 (92) [quinuclidine – C_4H_7], 136 (100) [quinuclidine], 293.3 (89) [M]

Optical rotary power:

$[\alpha]_D$ = 132°, $[\alpha]_{578}$ = 139°, $[\alpha]_{546}$ = 160°, $[\alpha]_{436}$ = 293° (c = 0.63, $CHCl_3$)

Elemental analysis:	calcd.:	C 77.78	H 7.90	N 14.32
	found:	C 77.39	H 7.97	N 14.17

5.4.2 General procedure for the synthesis of the amides of 9-amino(9-deoxy)epicinchonine (29)

29 was dissolved in the given amount of CH_2Cl_2 and NEt_3. Then a solution of the appropriate benzoyl chloride in CH_2Cl_2 was added dropwise at 0 °C. After stirring for 10 h at room temp., the reaction mixture was diluted with CH_2Cl_2 and washed 3 × with half-concentrated Na_2CO_3 solution, dried over Na_2CO_3 and evaporated.

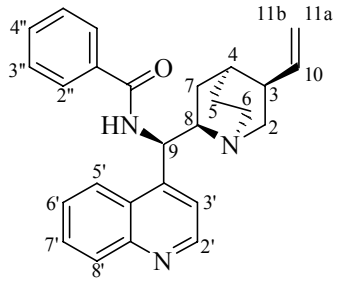
Amides **30**, **32**, **33**, **35**, **37**, **38** were transformed into the hydrochloride before chromatography. This was done by stirring the crude product with an excess of ethanolic HCl for 10 h. After removal of the solvent, the hydrochloride was recrystallized or precipitated as described. The free base was liberated by dissolving the hydrochloride in water, adding an excess of saturated Na_2CO_3 solution and extraction with CH_2Cl_2.

All the amides were purified by chromatography on silica gel with MeOH as eluent. As after evaporation of the chromatography fractions often foams resulted, recrystallisation was carried out in most cases. Further details are given for the individual compounds.

Some amide derivatives included water affecting elemental analyses but showing up in the ^1H NMR spectra.

5.4.2.1 *N*-(9-Deoxyepicinchonine-9-yl)benzamide (30)[51]

29 (800 mg, 2.73 mmol), CH_2Cl_2 (20 mL), NEt_3 (5.5 mL) and benzoyl chloride (507.5 mg, 3.61 mmol), CH_2Cl_2 (5 mL). The hydrochloride was dissolved in MeOH, precipitated with acetone and stored at –30 °C.



$C_{26}H_{27}N_3O$ (397.5)

Yield: 280 mg (0.70 mmol, 26%), colorless solid

Mp: 95–96 °C (lit. 93 °C)

IR (KBr): ν [cm^{-1}] = 3480m, 3320m, 3200 (N–H); 3060m, 3950m, 2880m (C–H); 1630s (amide I); 1580s, (C=C); 1540s (amide II)

^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm] = 0.97–1.12 (m, 1 H, H7b), 1.35–1.65 (m, 4 H, H4, H5, H7a), 2.27–2.43 (m, 1 H, H3), 2.85–3.29 (m, 5 H, H2, H6, H8), 5.15 (td, ^3J = 17.3 Hz, ^2J = 1.4 Hz, ^4J = 1.4 Hz, 1 H, H11b), 5.17 (td, ^3J = 10.7 Hz, ^2J = 1.4 Hz, ^4J = 1.4 Hz, 1 H, H11a), 5.48 (br s, 1 H, H9), 5.94 (ddd, ^3J = 17.1 Hz, ^3J = 10.6 Hz, ^3J = 6.5 Hz, 1 H, H10), 7.38–7.50 (m, 3 H, H3'', H4''), 7.53 (d, ^3J = 4.7 Hz, 1 H, *H3'*), 7.57–7.67 (m, 1 H, H6'), 7.68–7.78 (m, 1 H, H7'), 7.84 (dd, ^3J = 8.1 Hz, ^4J = 1.2 Hz, 2 H, H2''), 8.03 (br s, 1 H, NH), 8.14 (dd, ^3J = 8.5 Hz, ^4J = 1.1 Hz, 1 H, H8'), 8.45 (d, ^3J = 8.0 Hz, 1 H, H5'), 8.88 (d, ^3J = 4.4 Hz, 1 H, H2')

MS (EI, 70eV): *m/z* (%) = 105 (100) [PhCO], 136.1 (76) [quinuclidine], 276.2 (73) [M – PhCO], 397.2 (44) [M]

Optical rotary power:

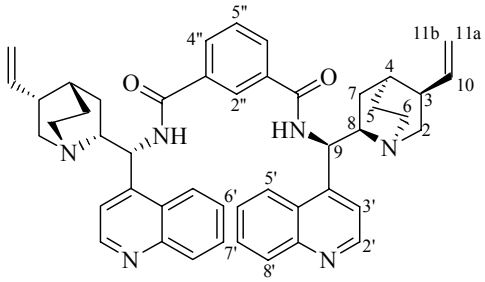
$[\alpha]_D$ = 261°, $[\alpha]_{578}$ = 288°, $[\alpha]_{546}$ = 333°, $[\alpha]_{436}$ = 630° (c = 0.51, $CHCl_3$)

Elemental analysis:

calcd. for $C_{26}H_{27}N_3O \cdot 0.5\ H_2O$:	C 76.82	H 6.94	N 10.33
found:	C 76.27	H 6.89	N 10.20

5.4.2.2 *N,N´*-Bis(9-deoxyepicinchonine-9-yl)isophthalamide (31)[51]

29 (1.62 g, 5.53 mmol), CH_2Cl_2 (25 mL), NEt_3 (10 mL) and isophthalic acid chloride[117] (555.3 mg, 2.74 mmol), CH_2Cl_2 (5 mL). The crude product was taken up with CH_2Cl_2 and precipitated with Et_2O.



$C_{46}H_{48}N_6O_2$ (716.9)

Yield: 550 mg (0.77 mmol, 14%), colorless solid

Mp: 216–218 °C (lit. 224 °C)

IR (KBr): ν [cm^{-1}] = 3380m (N–H), 3080w, 2960s, 2880s (C–H), 1660s (amide I), 1590m, 1570w (C=C), 1510s (amide II)

^{1}H NMR (250 MHz, $CDCl_3$): δ [ppm] = 0.83–1.08 (m, 2 H, H7b), 1.30–1.72 (m, 8 H, H4, H5, H7a), 2.22–2.39 (m, 2 H, H3), 2.73–3.19 (m, 10 H, H2, H6, H8), 5.11 (td, ^3J = 17.2 Hz, ^2J = 1.5 Hz, ^4J = 1.5 Hz, 2 H, H11b), 5.18 (td, ^3J = 10.5 Hz, ^2J = 1.4 Hz, ^4J = 1.4 Hz, 2 H, H11a), 5.40 (br s, 2 H, H9), 5.93 (ddd, ^3J = 17.2 Hz, ^3J = 10.5 Hz, ^3J = 6.4 Hz, 2 H, H10), 7.45 (d, ^3J = 4.8 Hz, 2 H, H3'), 7.51 (d, ^3J = 7.7 Hz, 1 H, H5''), 7.55–7.66 (m, 2 H, H6'), 7.67–7.78 (m, 2 H, H7'), 7.94 (dd, ^3J = 7.7 Hz, ^4J = 1.7 Hz, 2 H, H4''), 8.00 (br s, 2 H, NH), 8.14 (dd, ^3J = 8.4 Hz, ^4J = 1.2 Hz, 2 H, H8'), 8.31 (t, ^4J = 1.6 Hz, 1 H, H2''), 8.41 (d, ^3J = 8.2 Hz, 2 H, H5'), 8.85 (d, ^3J = 4.5 Hz, 2 H, H2')

MS (PI-DCI, NH_3): *m/z* (%) = 277.6 (100) [$C_{19}H_{21}N_2$], 717.7 (14) [MH]

Optical rotary power:

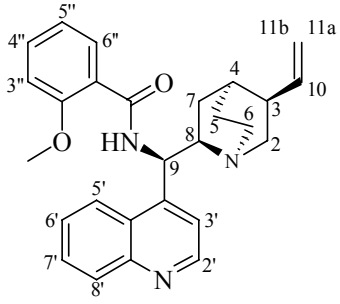
$[\alpha]_D$ = 254°, $[\alpha]_{578}$ = 265°, $[\alpha]_{546}$ = 318°, $[\alpha]_{436}$ = 602° (c = 0.92, $CHCl_3$)

Elemental analysis:

calcd. for $C_{46}H_{48}N_6O_3 \cdot 1.5\ H_2O$:	C 74.27	H 6.91	N 11.30
found:	C 74.24	H 6.58	N 11.34

5.4.2.3 *N*-(9-Deoxyepicinchonine-9-yl)-2-methoxybenzamide (32)[25]

29 (1.00 g, 3.41 mmol), CH_2Cl_2 (18 mL), NEt_3 (7 mL) and 2-methoxybenzoyl chloride[118] (1.00 g, 5.86 mmol), CH_2Cl_2 (4 mL). The hydrochloride was dissolved in MeOH, precipitated with acetone and stored at –30 °C.



$C_{27}H_{29}N_3O_2$ (427.5)

Yield: 420 mg (0.98 mmol, 29%), colorless solid

Mp: 79–80 °C (lit. 83–84 °C)

IR (KBr): ν [cm^{-1}] = 3380m (N–H), 3080w, 2940m, 2880w (C–H); 1660s (amide I); 1600s (C=C); 1510s (amide II)

^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm] = 0.80–1.02 (m, 1 H, H7b), 1.21–1.62 (m, 4 H, H4, H5, H7a), 2.25–2.38 (m, 1 H, H3), 2.85–3.18 (m, 5 H, H2, H6, H8), 4.00 (s, 3 H, OCH_3), 5.14 (td, ^3J = 17.4 Hz, ^2J = 1.5 Hz, ^4J = 1.5 Hz, 1 H, H11b), 5.16 (td, ^3J = 10.6 Hz, ^2J = 1.4 Hz, ^4J = 1.4 Hz, 1 H, H11a), 5.48 (br d, 1 H, H9), 5.94 (ddd, ^3J = 17.2 Hz, ^3J = 10.6 Hz, ^3J = 6.6 Hz, 1 H, H10), 6.94–7.02 (m, 2 H, H3'', H5''), 7.44–7.36 (m, 1 H, H4''), 7.48 (d, ^3J = 4.6 Hz, 1 H, H3'), 7.54–7.64 (m, 1 H, H6'), 7.66–7.75 (m, 1 H, H7'), 7.99 (dd, ^3J = 8.2 Hz, ^4J = 1.9 Hz, 1 H, H6''), 8.12 (dd, ^3J = 8.5 Hz, ^4J = 1.1 Hz, 1 H, H8'), 8.45 (dd, ^3J = 8.6 Hz, ^4J = 0.9 Hz, 1 H, H5'), 8.86 (d, ^3J = 4.6 Hz, 1 H, H2'), 9.33 (br s, 1 H, NH)

MS (EI, 70eV): *m/z* (%) = 135.0 (100) [2-MeO-PhCO], 276.2 (41) [M – 2-MeO-PhCONH], 292.1 (23) [M – quinuclidine], 427.3 (23) [M]

Optical rotary power:

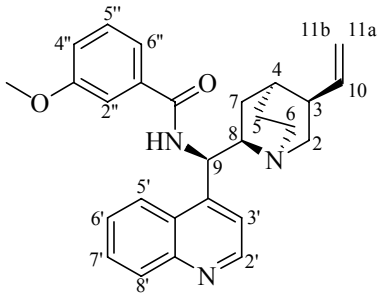
$[\alpha]_D$ = 312°, $[\alpha]_{578}$ = 320°, $[\alpha]_{546}$ = 378°, $[\alpha]_{436}$ = 741° (c = 0.47, $CHCl_3$)

Elemental analysis:

calcd. for $C_{27}H_{29}N_3O_2 \cdot 0.5\ H_2O$:	C 74.29	H 6.93	N 9.63
found:	C 74.64	H 6.89	N 9.74

5.4.2.4 *N*-(9-Deoxyepicinchonine-9-yl)-3-methoxybenzamide (33)[25]

29 (1.00 g, 3.41 mmol), CH_2Cl_2 (18 mL), NEt_3 (7 mL) and 3-methoxybenzoyl chloride[118] (1.00 g, 5.86 mmol), CH_2Cl_2 (4 mL). The hydrochloride was dissolved in MeOH, precipitated with acetone and stored at –30 °C. The free base was crystallized from Et_2O.



$C_{27}H_{29}N_3O_2$ (427.5)

Yield: 300 mg (0.70 mmol, 21%), colorless solid

Mp: 80–82 °C (lit. 81–83 °C)

IR (KBr): ν [cm^{-1}] = 3480m, 3340m, 3220 (N–H); 3100m, 3080m, 3940m, 2880m (C–H); 1640s (amide I); 1600s, 1580s, (C=C); 1530s (amide II)

^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm] = 0.95–1.11 (m, 1 H, H7b), 1.33–1.75 (m, 4 H, H4, H5, H7a), 2.26–2.42 (m, 1 H, H3), 2.81–3.29 (m, 5 H, H2, H6, H8), 3.80 (s, 3 H, OCH_3), 5.14 (td, ^3J = 17.2 Hz, ^2J = 1.5 Hz, ^4J = 1.5 Hz, 1 H, H11b), 5.20 (td, ^3J = 10.9 Hz, ^2J = 1.5 Hz, ^4J = 1.5 Hz, 1 H, H11a), 5.45 (br s, 1 H, H9), 5.94 (ddd, ^3J = 17.1 Hz, ^3J = 10.6 Hz, ^3J = 6.5 Hz, 1 H, H10), 6.99–7.07 (m, 1 H, H4''), 7.30–7.43 (m, 3 H, H2'', H5'', H6''), 7.52 (d, ^3J = 4.8 Hz, 1 H, H3'), 7.57–7.66 (m, 1 H, H6'), 7.67–7.77 (m, 1 H, H7'), 8.00 (br s, 1 H, NH), 8.13 (dd, ^3J = 8.2 Hz, ^4J = 1.1 Hz, 1 H, H8'), 8.44 (dd, ^3J = 8.6 Hz, ^4J = 0.9 Hz, 1 H, H5'), 8.87 (d, ^3J = 4.4 Hz, 1 H, H2')

MS (EI, 70eV): *m/z* (%) = 135.0 (100) [3-MeO-PhCO], 276.2 (76) [M – 3-MeO-PhCONH], 292.1 (41) [M – quinuclidine], 427.3 (49) [M]

Optical rotary power:

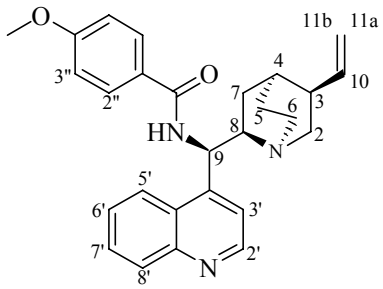
$[\alpha]_D$ = 273°, $[\alpha]_{578}$ = 281°, $[\alpha]_{546}$ = 325°, $[\alpha]_{436}$ = 620° (c = 0.53, $CHCl_3$)

Elemental analysis:

calcd. for $C_{27}H_{29}N_3O_2 \cdot 1\ H_2O$:	C 72.78	H 7.01	N 9.43
found:	C 72.96	H 6.67	N 9.45

5.4.2.5 *N*-(9-Deoxyepicinchonine-9-yl)-4-methoxybenzamide (34)[25]

29 (1.00 g, 3.41 mmol), CH_2Cl_2 (18 mL), NEt_3 (7 mL) and 4-methoxybenzoyl chloride (1.00 g, 5.86 mmol), CH_2Cl_2 (4 mL). The free base was recrystallized from Et_2O.



$C_{27}H_{29}N_3O_2$ (427.5)

Yield: 450 mg (1.05 mmol, 31%), colorless solid

Mp: 138–140 °C (lit. 135–137 °C)

IR (KBr): ν [cm^{-1}] = 3340m (N–H); 3080w, 2950s, 2880m (C–H); 1640s (amide I); 1610s, 1580s, 1540s (C=C); 1510s (amide II)

^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm] = 0.91–1.06 (m, 1 H, H7b), 1.34–1.71 (m, 4 H, H4, H5, H7a), 2.24–2.37 (m, 1 H, H3), 2.77–3.16 (m, 5 H, H2, H6, H8), 3.83 (s, 3 H, OCH_3), 5.12 (td, ^3J = 17.2 Hz, ^2J = 1.5 Hz, ^4J = 1.5 Hz, 1 H, H11b), 5.17 (td, ^3J = 10.5 Hz, ^2J = 1.4 Hz, ^4J = 1.4 Hz, 1 H, H11a), 5.38 (br d, 1 H, H9), 5.93 (ddd, ^3J = 17.2 Hz, ^2J = 10.6 Hz, ^3J = 6.6 Hz, 1 H, H10), 6.91 (d, ^3J = 8.8 Hz, 2 H, H3''), 7.49 (d, ^3J = 4.6 Hz, 1 H, H3'), 7.56–7.63 (m, 1 H, H6'), 7.67–7.81 (m, 2 H, H7', NH), 7.77 (d, ^3J = 8.9 Hz, 2 H, H2''), 8.13 (dd, ^3J = 8.4 Hz, ^4J = 1.1 Hz, 1 H, H8'), 8.44 (dd, ^3J = 8.6 Hz, ^4J = 0.9 Hz, 1 H, H5'), 8.86 (d, ^3J = 4.5 Hz, 1 H, H2')

MS (EI, 70eV): *m/z* (%) = 135.0 (100) [4-MeO-PhCO], 276.2 (45) [M – 4-MeO-PhCONH], 292.1 (22) [M – quinuclidine], 427.3 (23) [M]

Optical rotary power:

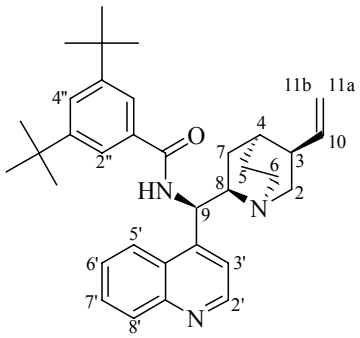
$[\alpha]_D$ = 293°, $[\alpha]_{578}$ = 307°, $[\alpha]_{546}$ = 356°, $[\alpha]_{436}$ = 685° (c = 0.51, $CHCl_3$)

Elemental analysis:

calcd. for $C_{27}H_{29}N_3O_2 \cdot 0.5\ H_2O$:	C 74.29	H 6.93	N 9.63
found:	C 74.29	H 6.65	N 9.56

5.4.2.6 *N*-(9-Deoxyepicinchonine-9-yl)-3,5-di-*tert*-butylbenzamide (35)[25]

29 (1.00 g, 3.41 mmol), CH_2Cl_2 (18 mL), NEt_3 (7 mL) and 3,5-di-*tert*-butylbenzoyl chloride[118] (1.07 g, 4.23 mmol), CH_2Cl_2 (4 mL). The hydrochloride was dissolved in MeOH, precipitated with Et_2O and stored at –30 °C. The free base was recrystallized from Et_2O.



$C_{34}H_{43}N_3O$ (509.7)

Yield: 520 mg (0.70 mmol, 30%), colorless solid

Mp: 208–210 °C (lit. 209–210 °C)

IR (KBr): ν [cm^{-1}] = 3380m (N–H); 3080w, 2960s, 2880m (C–H); 1650s (amide I), 1590s, 1570w (C=C); 1510m (amide II)

^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm] = 0.94–1.09 (m, 1 H, H7b), 1.34 (s, 18 H, CH_3), 1.38–1.74 (m, 4 H, H4, H5, H7a), 2.27–2.40 (m, 1 H, H3), 2.79–3.20 (m, 5 H, H2, H6, H8), 5.13 (td, ^3J = 17.3 Hz, ^2J = 1.6 Hz, ^4J = 1.6 Hz, 1 H, H11b), 5.19 (td, ^3J = 10.6 Hz, ^2J = 1.4 Hz, ^4J = 1.4 Hz, 1 H, H11a), 5.43 (br d, 1 H, H9), 5.95 (ddd, ^3J = 17.2 Hz, ^3J = 10.6 Hz, ^3J = 6.6 Hz, 1 H, H10), 7.54 (d, ^3J = 4.4 Hz, 1 H, H3'), 7.57 (t, ^3J = 1.8 Hz, 1 H, H4''), 7.58–7.64 (m, 1 H, H6'), 7.64 (d, ^3J = 1.6 Hz, 2 H, H2''), 7.68–7.77 (m, 1 H, H7'), 7.89 (br s, 1 H, NH), 8.14 (dd, ^3J = 8.5 Hz, ^4J = 1.1 Hz, 1 H, H8'), 8.47 (d, ^3J = 8.2 Hz, 1 H, H5'), 8.88 (d, ^3J = 4.7 Hz, 1 H, H2')

MS (PI-EI, 70 eV): *m/z* (%) = 217.1 (75) [3,5-di-tert-butyl-PhCO], 276.1 (100) [M – 3,5-di-tert-butyl-PhCONH], 509 (40) [M]

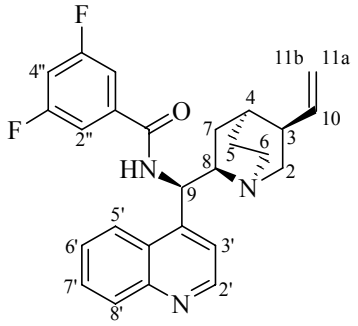
Optical rotary power:

$[\alpha]_D$ = 251°, $[\alpha]_{578}$ = 267°, $[\alpha]_{546}$ = 309°, $[\alpha]_{436}$ = 571° (c = 0.32, $CHCl_3$)

Elemental analysis:	calcd.:	C 80.12	H 8.50	N 8.24
	found:	C 79.76	H 8.50	N 8.21

5.4.2.7 *N*-(9-Deoxyepicinchonine-9-yl)-3,5-difluorobenzamide (36)

29 (848 mg, 2.89 mmol), CH_2Cl_2 (15 mL), NEt_3, (6 mL) and 3,5-difluorobenzoyl chloride (748 mg, 4.24 mmol), CH_2Cl_2 (4 mL). Recrystallization from Et_2O.



$C_{26}H_{25}F_2N_3O$ (433.5)

Yield: 326 mg (0.75 mmol, 26%), colorless solid

Mp: 134–137 °C

IR (KBr): ν [cm^{-1}] = 3320m, 3230m (N–H); 3100m, 3060m, 2940s, 2880m (C–H); 1640s (amide I); 1595s, 1545s (C=C); 1515s (amide II)

^{1}H NMR (250 MHz, $CDCl_3$): δ [ppm] = 0.95–1.09 (m, 1 H, H7b), 1.30–1.71 (m, 4 H, H4, H5, H7a), 2.25–2.41 (m, 1 H, H3), 2.89–3.18 (m, 5 H, H2, H6, H8), 5.12 (td, ^3J = 17.6 Hz, ^2J = 1.7 Hz, ^4J = 1.7 Hz, 1 H, H11b), 5.18 (td, ^3J = 10.8 Hz, ^2J = 1.7 Hz, ^4J = 1.7 Hz, 1 H, H11a), 5.36 (br d, 1 H, H9), 5.93 (ddd, ^3J = 17.1 Hz, ^3J = 10.6 Hz, ^3J = 6.4 Hz, 1 H, H10), 6.93 (tt, $^3J_{H4'',F}$ = 8.6 Hz, ^4J = 2.3 Hz, 1 H, H4''), 7.27–7.34 (m, 2 H, H2''), 7.46 (d, ^3J = 4.4 Hz, 1 H, H3'), 7.56–7.67 (m, 1 H, H6'), 7.68–7.79 (m, 1 H, H7'), 7.87 (br s, 1 H, NH), 8.15 (dd, ^3J = 8.3 Hz, ^4J = 1.2 Hz, 1 H, H8'), 8.39 (d, ^3J = 7.9 Hz, 1 H, H5'), 8.88 (d, ^3J = 4.4 Hz, 1 H, H2')

MS (EI, 70eV): *m/z* (%) = 136.3 (100) [quinuclidine], 141.2 (62) [3,5-di-F-PhCO], 433.1 (10) [M]

Optical rotary power:

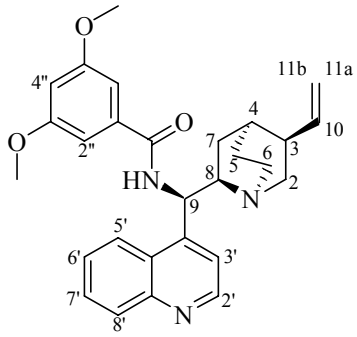
$[\alpha]_D$ = 243°, $[\alpha]_{578}$ = 270°, $[\alpha]_{546}$ = 311°, $[\alpha]_{436}$ = 588° (c = 0.54, $CHCl_3$)

Elemental analysis:

calcd. for $C_{26}H_{25}F_2N_3O \cdot 2.2\ H_2O$:	C 69.22	H 6.57	N 9.31
found:	C 68.94	H 6.09	N 9.16

5.4.2.8 *N*-(9-Deoxyepicinchonine-9-yl)-3,5-dimethoxybenzamide (37)

29 (590 mg, 2.01 mmol), CH_2Cl_2 (12 mL), NEt_3 (4.1 mL) and 3,5-dimethoxybenzoyl chloride[118] (522 mg, 2.60 mmol), CH_2Cl_2 (3 mL). The hydrochloride was dissolved in MeOH, precipitated with acetone and stored at –30 °C. The free base was recrystallized from Et_2O.



$C_{28}H_{31}N_3O_3$ (457.6)

Yield: 330 mg (0.72 mmol, 36%), Colorless solid

Mp: 123–125 °C

IR (KBr): ν [cm^{-1}] = 3340m (N–H); 3100w, 3020w, 2950m, 2880w, 2860w (C–H); 1600s (amide I); 1535s (C=C); 1515m (amide II)

^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm] = 0.91–1.07 (m, 1 H, H7b) , 1.46–1.73 (m, 4 H, H4, H5, H7a), 2.24–2.38 (m, 1 H, H3), 2.76–3.15 (m, 5 H, H2, H6, H8), 3.79 (s, 6 H, OCH_3), 5.12 (td, ^3J = 17.3 Hz, ^2J = 1.5 Hz, ^4J = 1.5 Hz, 1 H, H11b), 5.18 (td, ^3J = 10.6 Hz, ^2J = 1.4 Hz, ^4J = 1.4 Hz, 1 H, H11a), 5.93 (ddd, ^3J = 17.2 Hz, ^3J = 10.6 Hz, ^3J = 6.4 Hz, 1 H, H10), 6.57 (t, ^4J = 1.8 Hz, 1 H, H4''), 6.95 (d, ^4J = 2.2 Hz, 2 H, H2''), 7.48 (d, ^3J = 4.4 Hz, 1 H, H3'), 7.55–7.66 (m, 1 H, H6'), 7.67–7.77 (m, 1 H, H7'), 7.90 (br s, 1 H, NH), 8.13 (dd, ^3J = 8.4 Hz, ^{4}J = 1.0 Hz, 1 H, H8'), 8.47 (d, ^3J = 8.0 Hz, 1 H, H5'), 8.87 (d, ^3J = 4.7 Hz, 1 H, H2')

MS (EI, 70eV): *m/z* (%) = 165.2 (100) [3,5-di-MeO-PhCO], 276.3 (84) [M – 3,5-di-MeO-PhCONH], 457.2 (45) [M]

Optical rotary power:

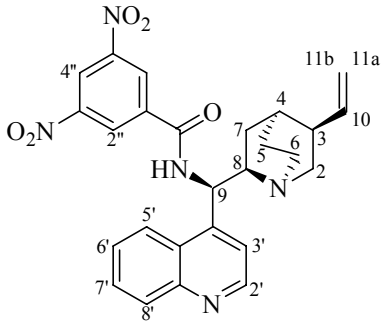
$[\alpha]_D$ = 267°, $[\alpha]_{578}$ = 274°, $[\alpha]_{546}$ = 318°, $[\alpha]_{436}$ = 610° (c = 0.52, $CHCl_3$)

Elemental analysis:

calcd. for $C_{28}H_{31}N_3O_3 \cdot H_2O$:	C 70.71	H 6.99	N 8.84
found:	C 70.30	H 6.94	N 8.76

5.4.2.9 *N*-(9-Deoxyepicinchonine-9-yl)-3,5-dinitrobenzamide (38)

As the acid chloride is almost insoluble in CH_2Cl_2, $CHCl_3$ was used for this batch. **29** (500 mg, 1.70 mmol), $CHCl_3$ (9 mL), NEt_3 (3.5 mL) and 3,5-dinitrobenzoyl chloride (575 mg, 2.49 mmol), $CHCl_3$ (20 mL). The hydrochloride was dissolved in MeOH and precipitated with Et_2O (–30 °C).



$C_{26}H_{25}N_5O_5$ (487.5)

Yield: 190 mg (0.39 mmol, 23%), yellow-brown solid

Mp: 196–199 °C

IR (KBr): ν [cm^{-1}] = 3320m (N–H); 3100m, 2940s, 2870m (C–H); 1660s, 1640s (amide I); 1590m (C=C); 1540s (amide II)

^{1}H NMR (250 MHz, $CDCl_3$): δ [ppm] = 0.77–0.97 (m, 1 H, H7b), 0.97–1.76 (m, 4 H, H4, H5, H7a), 2.27–2.42 (m, 1 H, H3), 2.73–3.28 (m, 5 H, H2, H6, H8), 5.14 (td, ^3J = 17.2 Hz, ^2J = 1.5 Hz, ^4J = 1.5 Hz, 1 H, H11b), 5.21 (td, ^3J = 10.5 Hz, ^2J = 1.4 Hz, ^4J = 1.4 Hz, 1 H, H11a), 5.46 (br s, 1 H, H9), 5.94 (ddd, ^3J = 17.1 Hz, ^3J = 10.5 Hz, ^3J = 6.5 Hz, 1 H, H10), 7.46 (d, ^3J = 4.4 Hz, 1 H, H3'), 7.61–7.71 (m, 1 H, H6'), 7.71–7.81 (m, 1 H, H7'), 8.14 (dd, ^3J = 8.5 Hz, ^4J = 1.2 Hz, 1 H, H8'), 8.38 (dd, ^3J = 8.4 Hz, ^4J = 0.8 Hz, 1 H, H5'), 8.87 (d, ^3J = 4.4 Hz, 1 H, H2'), 8.93 (d, ^4J = 2.1 Hz, 2 H, H2''), 9.13 (t, ^4J = 2.1 Hz, 1 H, H4'')

MS (EI, 70eV): *m/z* (%) = 43.2 (37) [C_2H_5N], 136.3 (100) [quinuclidine], 487.1 (14) [M]

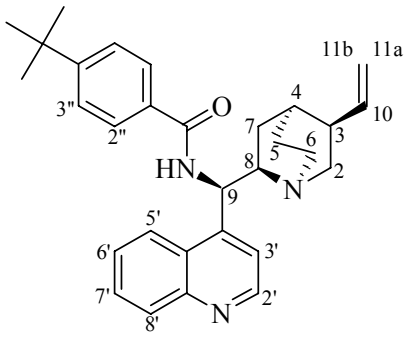
Optical rotary power:

$[\alpha]_D$ = 236°, $[\alpha]_{578}$ = 248°, $[\alpha]_{546}$ = 286°, $[\alpha]_{436}$ = 541° (c = 0.51, $CHCl_3$)

Elemental analysis:	calcd.:	C 64.06	H 5.17	N 14.37
	found:	C 63.74	H 5.60	N 14.40

5.4.2.10 *N*-(9-Deoxyepicinchonine-9-yl)-4-*tert*-butylbenzamide (39)

29 (908 mg, 3.09 mmol), CH_2Cl_2 (16 mL), NEt_3 (6.4 mL) and 4-*tert*-butylbenzoyl chloride (755 mg, 3.84 mmol), CH_2Cl_2 (4 mL). After dissolution in Et_2O the product was precipitated with PE 40/60 and stored at –30 °C.



$C_{30}H_{35}N_3O$ (453.6)

Yield: 390 mg (0.86 mmol, 28%), colorless solid

Mp: 122–124 °C

IR (KBr): ν [cm^{-1}] = 3280m (N–H); 3100m, 2960s, 2880s (C–H); 1640s (amide I); 1600m, 1555 (C=C); 1515 (amide II)

^{1}H NMR (250 MHz, $CDCl_3$): δ [ppm] = 0.90–1.10 (m, 1 H, H7b), 1.32 (s, 9 H, CH_3), 1.19–1.71 (m, 4 H, H4, H5, H7a), 2.23–2.38 (m, 1 H, H3), 2.76–3.17 (m, 5 H, H2, H6, H8), 5.12 (td, ^3J = 17.2 Hz, ^3J = 1.5 Hz, ^4J = 1.5 Hz, 1 H, H11b), 5.17 (td, ^3J = 10.6 Hz, ^3J = 1.5 Hz, ^4J = 1.5 Hz, 1 H, H11a), 5.38 (br d, 1 H, H9), 5.93 (ddd, ^3J = 17.1 Hz, ^3J = 10.6 Hz, ^3J = 6.5 Hz, 1 H, H10), 7.45 (d , ^3J = 8.7 Hz, 2 H, H3'', H5''), 7.49 (d, ^3J = 4.6 Hz, 1 H, H3'), 7.55–7.65 (m, 1 H, H6'), 7.67–7.75 (m, 1 H, H7'), 7.75 (d, ^3J = 8.7 Hz, 2 H, H2'', H6''), 7.90 (s, 1 H, NH), 8.13 (dd, ^3J = 8.4 Hz, ^4J = 1.2 Hz, 1 H, H8'), 8.45 (dd, ^3J = 8.5 Hz, ^4J = 1.0 Hz, 1 H, H5'), 8.86 (d, ^3J = 4.6 Hz, 1 H, H2')

MS (PI-EI, 70eV): *m/z* (%) = 161.3 (100) [4-*tert*-butyl-PhCO], 276.4 (88) [M – 4-*tert*-butyl-PhCONH], 453.6 (38) [M]

Optical rotary power:

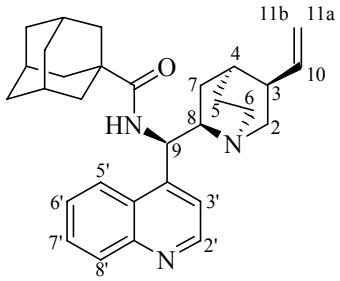
$[\alpha]_D$ = 266°, $[\alpha]_{578}$ = 279°, $[\alpha]_{546}$ = 322°, $[\alpha]_{436}$ = 616° (c = 0.53, $CHCl_3$)

Elemental analysis:

calcd. for $C_{30}H_{35}N_3O \cdot 1.2\ H_2O$:	C 75.82	H 7.93	N 8.84
found:	C 75.45	H 8.17	N 8.84

5.4.2.11 *N*-(9-Deoxyepicinchonine-9-yl)-adamantanecarboxamide (40)

29 (1.07 g, 3.66 mmol), CH_2Cl_2 (18 mL), NEt_3 (7 mL) and 1-adamantanecarboxylic acid chloride (884 mg, 4.45 mmol), CH_2Cl_2 (4 mL).



$C_{30}H_{37}N_3O$ (455.6)

Yield: 910 mg (2.00 mmol, 55%), colorless solid

Mp: 81–82 °C

IR (KBr): ν [cm^{-1}] = 3660m (N–H); 3080w, 2910s, 2860s (C–H); 1650s (amide I); 1590m, 1570w; 1510s (amide II)

^{1}H NMR (250 MHz, $CDCl_3$): δ [ppm] = 0.79–1.05 (m, 1 H, H7b), 1.29–1.91 (m, 19 H, H4, H5, H7a, adamantane-H), 2.20–2.39 (m, 1 H, H3), 2.64–2.81 (m, 1 H, H2), 2.85–3.08 (m, 4 H, H2, H6, H8), 5.09 (br s, 1 H, H9), 5.10 (td, ^3J = 17.3 Hz, ^2J = 1.5 Hz, ^4J = 1.5 Hz, 1 H, H11b), 5.16 (td, ^3J = 10.6 Hz, ^2J = 1.5 Hz, ^4J = 1.5 Hz, 1 H, H11a), 5.92 (ddd, ^3J = 17.1 Hz, ^3J = 10.4 Hz, ^3J = 6.6 Hz, 1 H, H10), 7.37 (d, ^3J = 4.8 Hz, 1 H, H3'), 7.50–7.61 (m, 1 H, H6'), 7.64–7.74 (m, 1 H, H7'), 8.10 (dd, ^3J = 8.5 Hz, ^4J = 1.0 Hz, 1 H, H8'), 8.35 (dd, ^3J = 8.7 Hz, ^4J = 0.8 Hz, 1 H, H5'), 8.84 (d, ^3J = 4.4 Hz, 1 H, H2')

MS (FD, CH_2Cl_2): *m/z* (%) = 455.5 (100) [M]

Optical rotary power:

$[\alpha]_D$ = 192°, $[\alpha]_{578}$ = 194°, $[\alpha]_{546}$ = 223°, $[\alpha]_{436}$ = 414° (c = 0.51, $CHCl_3$)

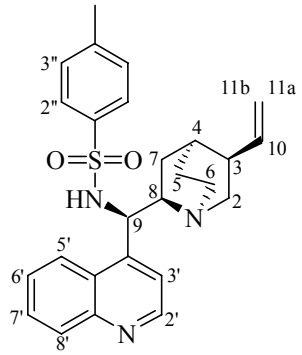
Elemental analysis:

calcd. for $C_{30}H_{37}N_3O \cdot 1/3\ H_2O$:	C 78.06	H 8.22	N 9.10
found:	C 78.27	H 8.45	N 8.45

5.4.3 Further cinchona alkaloid derivatives

5.4.3.1 *N*-(9-Deoxyepicinchonine-9-yl)-4-methylbenzenesulfonamide (43)

29 (960 mg, 3.27 mmol), toluene-4-sulfonyl chloride (938 mg, 4.92 mmol) and K_2CO_3 (540 mg, 3.90 mmol) were stirred in CH_2Cl_2 (20 mL) at room temp. for 10 h. The reaction mixture was diluted with CH_2Cl_2, K_2CO_3 was removed by filtration and the solution was washed 3 × with saturated Na_2CO_3 solution. Chomatography on SiO_2 with EtOAc:MeOH (9:1).



$C_{26}H_{29}N_3O_2S$ (447.6)

Yield: 460 mg (1.03 mmol, 31%), colorless solid

Mp: 190–192 °C

IR (KBr): ν [cm^{-1}] = 3440w (N–H), 3140w, 3090m, 3070m, 2940s, 2870m, 2880m (C–H); 1650w, 1600s, 1580m, 1520s, 1460s (C=C); 1390s, 1330s, 1170s (sulfonamide)

^{1}H NMR (250 MHz, $CDCl_3$): *δ* [ppm] = δ = 0.71–0.93 (m, 1 H, H7b), 1.08–1.68 (m, 4 H, H4, H5, H7a), 2.35 (s, 3 H, CH_3), 2.13–2.42 (m, 1 H, H3), 2.62–2.97 (m, 3.7 H, H2, H6, H8), 3.17–3.31 (m, 0.3 H, H8), 4.20 (br d, ^3J = 10.7 Hz, 0.3 H, H11b), 4.82–4.96 (m, 1.7 H, H9, H11b), 5.12 (td, ^3J = 10.6 Hz, ^2J = 1.4 Hz, ^4J = 1.4 Hz, 1 H, H11a), 5.76 (ddd, ^3J = 17.2 Hz, ^3J = 10.6 Hz, ^3J = 5.8 Hz, 1 H, H10), 6.83 (d, ^3J = 8.1 Hz, 0.6 H, H3'', H5''), 7.07 (d, ^3J = 8.0 Hz, 1.4 H, H3'', H5''), 7.17 (d, ^3J = 4.3 Hz, 0.3 H, H3'), 7.33 (d, ^3J = 8.4 Hz, 0.6 H, H2'', H6''), 7.39–7.46 (m, 2.4 H, H2'', H3', H6'', H7'), 7.55–7.64 (m, 1 H, H6'), 7.68–7.77 (m, 0.7 H, H7'), 7.98 (d, ^3J = 8.4 Hz, 0.3 H, H8'), 8.04 (d, ^3J = 8.5 Hz, 0.7 H, H8'), 8.10 (dd, ^3J = 8.5 Hz, ^4J = 0.9 Hz, 0.7 H, H5'), 8.41 (d, ^3J = 8.4 Hz, 0.3 H, H5'), 8.71 (d, ^3J = 4.6 Hz, 0.7 H, H2'), 8.74 (d, ^3J = 4.2 Hz, 0.3 H, H2')

^{1}H NMR (400 MHz, $C_2D_2Cl_4$, 110 °C): δ [ppm] = 0.77–0.92 (m, 1 H, H7b), 1.12–1.23 (m, 1 H, H7a), 1.37–1.64 (m, 3 H, H4, H5), 2.15–2.31 (m, 1 H, H3), 2.24 (s, 3 H, CH_3), 2.43–2.57 (m, 1 H, H2), 2.76–3.12 (m, 4 H, H2, H6, H8), 4.75 (br s, 1 H, H9), 4.95 (td,

^3J = 17.4 Hz, ^2J = 1.5 Hz, ^4J = 1.5 Hz, 1 H, H11b), 5.12 (td, ^3J = 10.6 Hz, ^2J = 1.4 Hz, ^4J = 1.4 Hz, 1 H, H11a), 5.76 (ddd, ^3J = 17.3 Hz, ^3J = 10.7 Hz, ^3J = 5.9 Hz, 1 H, H10), 6.92 (d, ^3J = 7.9 Hz, 2 H, H3'', H5''), 7.21–7.38 (m, 1 H, H3'), 7.33 (d, ^3J = 8.3 Hz, 2 H, H2'', H6''), 7.43–7.54 (m, 1 H, H6'), 7.57–7.68 (m, 1 H, H7'), 8.03 (d, ^3J = 8.4 Hz, ^4J = 0.3 Hz, 1 H, H8'), 8.06–8.20 (m, 1 H, H5'), 8.68 (d, ^3J = 4.5 Hz, 1 H, H2')

MS (EI, 70eV): *m/z* (%) = 136.3 (100) [quinuclidine]; 292.3 (86) [M – 4-Me-PhSO$_2$], 447.1 (17) [M]

Optical rotary power:

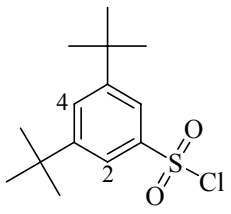
$[\alpha]_D$ = 52°, $[\alpha]_{578}$ = 55°, $[\alpha]_{546}$ = 62°, $[\alpha]_{436}$ = 108° (c = 0.51, $CHCl_3$)

Elemental analysis:	calcd.:	C 69.77	H 6.53	N 9.39
	found:	C 69.20	H 6.92	N 9.32

5.4.3.2 *N*-(9-Deoxyepicinchonine-9-yl)-3,5-di-*tert*-butylbenzenesulfonamide (44)

5.4.3.2.1 3,5-Di-*tert*-butylbenzenesulfonyl chloride (40)[69]

To 1,3,5-tri-*tert*-butylbenzene (5.00 g, 20.3 mmol) chlorosulfonic acid (13.3 mL, 65.4 mmol) was added dropwise at 0 °C. The resulting dark solution was stirred for 1 h at room temp. Then it was poured into ice-water, the resulting precipitate was washed and chromatographed on SiO_2 (EtOAc/hexane 1:24).



$C_{14}H_{21}ClSO_2$ (288.8)

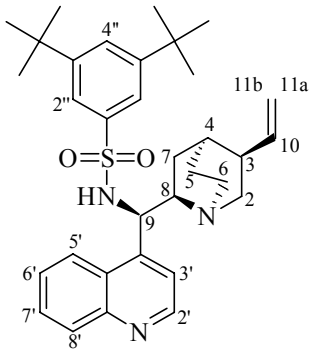
Yield: 3.17 g (11.0 mmol, 54.2%), colorless solid

bp: 90–92 °C (lit. 81–83 °C)

^{1}H NMR (250 MHz, $CDCl_3$): δ [ppm] = 1.52 (s, 18 H, CH_3), 7.71 (d, ^4J = 2.1 Hz, 2 H, H2), 7.90 (s, 1H, H4)

5.4.3.2.2 *N*-(9-Deoxyepicinchonine-9-yl)-3,5-di-*tert*-butylbenzenesulfonamide (44)

29 (650 mg, 2.22 mmol), 3,5-di-*tert*-butylbenzenesulfonyl chloride (962 mg, 3.33 mmol) and K_2CO_3 (360 mg, 2.60 mmol) in CH_2Cl_2 (20 mL) were stirred at room temp. for 10 h. The reaction mixture was diluted with CH_2Cl_2 and K_2CO_3 was filtered off. The organic layer was washed 3 × with saturated Na_2CO_3 solution. The crude product was chromatographed on SiO_2 with MeOH.



$C_{33}H_{43}N_3O_2S$ (545.8)

Yield: 340 g (0.62 mmol, 28%), colorless solid

Mp: 95–98 °C

IR (KBr): ν [cm^{-1}] = 3420w (N–H); 3200w, 3080w, 2960s, 2870m (C–H); 1640w, 1600m, 1575w, 1515m, 1480m, 1460m (C=C); 1370s, 1335s, 1170s (sulfonamide)

^{1}H NMR (250 MHz, $CDCl_3$): δ [ppm] = 0.65–0.88 (m, 1.7 H, H7a, H7b), 0.94–1.01 (m, 0.3 H, H7a), 1.04–1.66 (m, 3 H, H4, H5), 1.3 (s, 18 H, CH_3), 2.11–2.34 (m, 1 H, H3), 2.58–2.78 (m, 4.7 H, H2, H6, H8), 3.13–3.34 (m, 0.3 H, H8), 4.12 (d, ^3J = 10.7 Hz, 1 H, H11b), 4.75–4.92 (m, 2 H, H9, H11b), 5.00–5.11 (m, 1 H, H11a), 5.71 (ddd, ^3J = 17.3 Hz, ^3J = 10.7 Hz, ^3J = 5.4 Hz, 1 H, H10), 7.11 (d, ^3J = 4.3 Hz, 0.3 H, H3'), 7.36–7.40 (m, 0.3 H, H4''), 7.41–7.53 (m, 3.4 H, H2'', H3', H3'', H4''), 7.53–7.63 (m, 1 H, H6'), 7.66–7.76 (m, 1 H, H7'), 8.01 (d, ^3J = 8.5 Hz, 0.3 H, H8'), 8.06 (d, ^3J = 8.1 Hz, 0.7 H, H8'), 8.08 (dd, ^3J = 8.4 Hz, ^4J = 0.8 Hz, 0.7 H, H5'), 8.53 (d, ^3J = 8.3 Hz, 0.3 H, H5'), 8.72 (d, ^3J = 4.6 Hz, 0.7 H, H2'), 8.74 (d, ^3J = 4.5 Hz, 0.3 H, H2')

MS (FD, CH_2Cl_2): *m/z* (%) = 545.6 (100) [M]; 1090.9 (2) [2M]

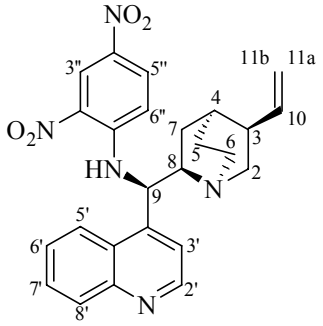
Optical rotary power:

$[\alpha]_D$ = 57°, $[\alpha]_{578}$ = 60°, $[\alpha]_{546}$ = 67°, $[\alpha]_{436}$ = 125° (c = 0.55, $CHCl_3$)

Elemental analysis:	calcd.:	C 72.62	H 7.94	N 7.70
	found:	C 72.20	H 8.00	N 7.44

5.4.3.3 *N*-(9-Deoxyepicinchonine-9-yl)-2,4-dinitrophenylamine (45)

29 (510 mg, 1.74 mmol) and 2,4-dinitrofluorobenzene (324 mg, 1.74 mmol) were stirred in CH_2Cl_2 (15 mL) at room temp. for 10 h. A yellow powder precipitated. The solvent was removed *in vacuo* and the residue was recrystallized from Et_2O.



$C_{25}H_{25}N_5O_4$ (459.5)

Yield: 400 mg (0.87 mmol, 50%), intensely yellow powder

Mp: 200–202 °C

IR (KBr): ν [cm^{-1}] = 3440w, 3280w (N–H); 3120w, 3090w, 2950s, 2890m (C–H); 1620s, 1590s, 1505s (C=C); 1455w, 1420w (C–H)

^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm] = 0.87–1.08 (m, 1 H, H7b), 1.34–1.79 (m, 4 H, H4, H5, H7a), 2.28–2.45 (m, 1 H, H3), 2.65–2.84 (m, 1 H, H2), 2.95–3.22 (m, 4 H, H2, H6, H8), 5.13 (td, ^3J = 17.3 Hz, ^2J = 1.5 Hz, ^4J = 1.5 Hz, 1 H, H11b), 5.21 (br td, 1 H, H 11a), 5.94 (ddd, 1H, ^3J = 17.2 Hz, ^3J = 8.8 Hz, ^3J = 6.3 Hz, 1 H, H10), 6.26 (br s, 1H, H9), 7.51 (d, ^3J = 4.5 Hz, 1 H, H3'), 7.65–7.93 (m, 3 H, H6'', H6', H7'), 7.85 (d, ^3J = 8.8 Hz, 1 H, H5''), 8.23 (d, ^3J = 7.8 Hz, 1 H, H8'), 8.33 (dd, ^3J = 8.6 Hz, ^4J = 0.6, 1 H, H5'), 8.90 (d, ^3J = 4.4 Hz, 1 H, H2'), 9.09 (d, ^4J = 2.7 Hz, 1 H, H3''), 9.84 (br s, 1 H, NH)

MS (EI, 70 eV): *m/z* (%) = 136.1 (100) [quinuclidine], 413.1 (19) [M – NO_2], 459.1 (30) [M]

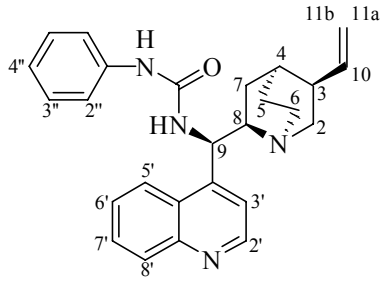
Optical rotary power:

$[\alpha]_D$ = 652°, $[\alpha]_{578}$ = 687°, $[\alpha]_{546}$ = 847° (c = 0.51, $CHCl_3$)

Elemental analysis:	calcd.:	C 65.35	H 5.48	N 15.24
	found:	C 65.02	H 5.49	N 14.99

5.4.3.4 *N*-(9-Deoxyepicinchonine-9-yl)-*N'*-phenylurea (46)

29 (276 mg, 0.94 mmol) was heated to 60 °C with phenylisocyanate (10 mL, 91.5 mmol) for 10 min. After further 15 min at room temp. the precipitate was collected, washed with PE 40/60 and recrystallized from Et_2O.



$C_{26}H_{28}N_4O$ (412.5)

Yield: 180 mg (0.44 mmol, 46%), colorless solid

Mp: 217–218 °C

IR (KBr): ν [cm^{-1}] = 3280m (N–H); 3190w, 3120w, 3070w, 2910m, 2060w (C–H); 1690s (amide I); 1550s, 1510m (amide II); 1495s, 1440m (C=C)

^{1}H NMR (250 MHz, $CDCl_3$): δ [ppm] = 0.80–0.97 (m, 1 H, H7b), 1.15–1.68 (m, 4 H, H4, H5, H7a), 2.19–2.36 (m, 1 H, H3), 2.77–3.06 (m, 5 H, H2, H6, H8), 5.10 (td, ^3J = 14.7 Hz, ^2J = 1.5 Hz, ^4J = 1.5 Hz, 1 H, H11b), 5.15 (td, ^3J = 14.7 Hz, ^2J = 1.5 Hz, ^4J = 1.5 Hz, 1 H, H11a), 5.30 (br d, 1 H, H9), 5.89 (ddd, ^3J = 17.1 Hz, ^3J = 10.5 Hz, ^3J = 6.6 Hz, 1 H, H10), 6.28 (br s, 1 H, RNH), 6.90–7.04 (m, 1 H, PhNH), 7.13–7.32 (m, 5 H, Ph), 7.47 (d, ^3J = 4.6 Hz, 1 H, H3'), 7.54–7.66 (m, 1 H, H6'), 7.67–7.77 (m, 1 H, H7'), 8.14 (dd, ^3J = 8.4 Hz, ^4J = 1.1 Hz, 1 H, H8'), 8.40 (dd, ^3J = 8.6 Hz, ^4J = 0.9 Hz, 1 H, H5'), 8.88 (d, ^3J = 4.6 Hz, 1 H, H2')

MS (EI, 70 eV): *m/z* (%) = 136.1 (100) [quinuclidine], 119.1 (72) [PhNCO], 412.0 (5) [M]

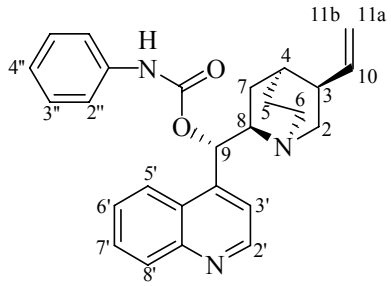
Optical rotary power:

$[\alpha]_D$ = 193°, $[\alpha]_{578}$ = 202°, $[\alpha]_{546}$ = 232°, $[\alpha]_{436}$ = 429° (c = 0.29, $CHCl_3$)

Elemental analysis:	calcd.:	C 75.70	H 6.84	N 13.58
	found:	C 75.52	H 6.86	N 13.48

5.4.3.5 Cinchonine-9-yl phenylcarbamate (47)[71]

Cinchonine (1.50 g, 5.10 mmol) was heated to 80 °C in phenylisocyanate (10 mL, 91.5 mmol) for 10 h. The excess of phenylisoyanate was removed *in vacuo*. The residue was stirred in boiling Et_2O, cooled to –30 °C and collected.



$C_{26}H_{27}N_3O_2$ (413.5)

Yield: 530 mg (1.25 mmol, 25%), colorless solid

Mp: 190–191 °C (Lit. 198 °C)

IR (KBr): ν [cm^{-1}] = 3440w (N–H); 3240w, 3200w, 3200w, 3130w, 2960s, 2880m (C–H); 1730s (amide I); 1620m, 1605m (C=C); 1560s (amide II); 1520m, 1500m (C–H)

^{1}H NMR (250 MHz, $CDCl_3$): δ [ppm] = 1.16–1.31 (m, 1H, H7b), 1.41–1.97 (m, 4 H, H4, H5, H7a), 2.20–2.34 (m, 1 H, H3), 2.61–2.90 (m, 2 H, H2, H6), 3.24–3.41 (m, 1 H, H8), 5.08 (td, ^3J = 9.7 Hz, ^2J = 1.5 Hz, ^4J = 1.5 Hz, 1 H, H11b), 5.12 (td, ^3J = 8.9 Hz, ^2J = 1.4 Hz, ^4J = 1.4 Hz, 1 H, H11a), 6.03 (ddd, ^3J = 17.1 Hz, ^3J = 10.5 Hz, ^3J = 7.2 Hz, 1 H, H10), 6.57 (d, ^3J = 8.0 Hz, 1 H, Ph-H), 6.82 (br s, 1 H, H9), 7.05 (t, ^3J = 7.2 Hz, 1 H, Ph-H), 7.19–7.39 (m, 3 H, Ph-H), 7.44 (d, ^3J = 4.5 Hz, 1 H, H3'), 7.54–7.64 (m, 1 H, H6'), 7.66–7.78 (m, 1 H, H7'), 8.13 (dd, ^3J = 8.4 Hz, ^4J = 0.7 Hz, 1 H, H8'), 8.25 (d, ^3J = 8.5 Hz, ^4J = 0.9 Hz, 1 H, H5'), 8.89 (d, ^3J = 4.5 Hz, 1 H, H2')

MS (EI, 70 eV): *m/z* (%) = 119.0 (46) [PhNCO], 136.1 (100) [quinuclidine], 413.1 (33) [M]

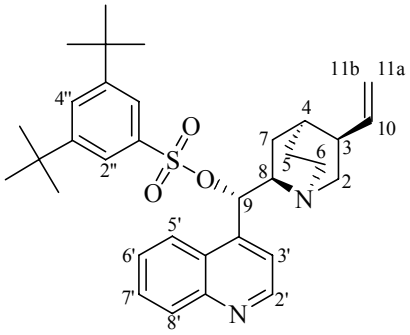
Optical rotary power:

$[\alpha]_D$ = 53°, $[\alpha]_{578}$ = 56°, $[\alpha]_{546}$ = 61°, $[\alpha]_{436}$ = 102° (c = 0.54, $CHCl_3$)

Elemental analysis:	calcd.:	C 75.52	H 6.58	N 10.16
	found:	C 75.00	H 6.49	N 10.27

5.4.3.6 Cinchonine-9-yl 3,5-di-*tert*-butylbenzenesulfonate (48)

Cinchonine (424 mg, 1.44 mmol) and NaH (40.8 mg, 1.70 mmol) were refluxed in THF (10 mL) for 2 h. The mixture was cooled to 0 °C, 3,5-di-tert-butylbenzenesulfonyl chloride (500 mg, 1.73 mmol) in THF (10 mL) was added dropwise. After refluxing for 10 h, the solvent was removed. The residue was taken up in 2 M HCl and the aqueous phase was washed 3 × with Et_2O. After making basic with 2 M NaOH, the aqueous phase was extracted 3 × with Et_2O. The combined organic layers were dried over Na_2SO_4 and evaporated. The slightly brown powder was washed with MeOH and recrystallized from Et_2O.



$C_{33}H_{42}N_2O_3S$ (546.8)

Yield: 300 mg (0.55 mmol, 39%), colorless solid

Mp: 180–182 °C

IR (KBr): ν [cm^{-1}] = 3070w, 2970s, 2940s, 2880s (C–H); 1600m, 1510m, 1480m, 1470m, 1455m (C=C); 1370s, 1360s (S=O); 1320m, 1250m; 1190s (S=O)

^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm] = 1.07 (s, 18 H, CH_3), 1.79–2.01 (m, 5 H, H4, H5, H7a, H7b), 2.19–2.33 (m, 1 H, H3), 2.54–3.40 (m, 5 H, H2, H6, H8), 5.06–5.17 (m, 2 H, H11a, H11b), 5.98 (ddd, ^3J = 16.5 Hz, ^3J = 10.8 Hz, ^3J = 7.6 Hz, 1 H, H10), 7.14 (m, 1H, H3'), 7.32 (t, ^4J = 1.8 Hz, 1 H, H4''), 7.35–7.42 (m, 2 H, H2''), 7.50–7.58 (m, 1 H, H6'), 7.61–7.69 (m, 1 H, H7'), 7.99 (dd, ^3J = 8.5 Hz, ^4J = 0.9 Hz, 1 H, H5'), 8.61 (d, ^3J = 4.5 Hz, 1 H, H2')

MS (DCI, NH_3): *m/z* (%) = 279.6 (100) [M – di-*tert*-butyl-$PhSO_2$], 547.4 (12) [MH]

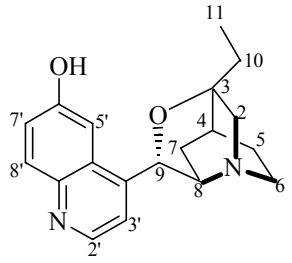
Optical rotary power:

$[\alpha]_D$ = 40°, $[\alpha]_{578}$ = 40°, $[\alpha]_{546}$ = 45°, $[\alpha]_{436}$ = 71° (c = 0.54, $CHCl_3$)

Elemental analysis:	calcd.:	C 72.49	H 7.74	N 5.12
	found:	C 72.25	H 7.59	N 5.17

5.4.3.7 (3*R*,8*R*,9*S*)-10,11-Dihydro-3,9-epoxy-6'-hydroxycinchonane (50)[72]

Quinidine (5.00 g, 15.4 mmol) and KBr (18.4 g, 159 mmol) were refluxed in H_3PO_4 (85%, 75 mL) for 7 d at 100 °C. The cool reaction mixture was dropped in KOH (25%, 500 mL) and adjusted to pH = 8 with aqueous NH_3. After 3 × extraction with $CHCl_3$, the residue was chromatographed on SiO_2 (MeOH:$CHCl_3$ 1:9 → 1:4). Recrystallisation from MeOH:H_2O (1:1).



$C_{19}H_{22}N_2O_2$ (310.4)

Yield: 1.55 g (4.99 mmol, 32%), colorless solid

Mp: 238–240 °C (lit. 258–259 °C)

IR (KBr): ν [cm^{-1}] = 3500–2200br (OH); 2960m, 2880m (C–H); 1640s, 1600m (C=C); 1510s, 1480s, 1490m, 1420m (C–H)

^{1}H NMR (250 MHz, $CDCl_3$): δ [ppm] = 1.05 (t, ^3J = 7.8 Hz, 3 H, H11), 1.22 (dd, ^3J = 12.5 Hz, ^3J = 6.9 Hz, 1 H, H7b), 1.53–1.81 (m, 2 H, H5), 1.69 (q, ^3J = 7.8 Hz, 2 H, H10), 1.87 (ddd, ^3J = 12.9 Hz, ^3J = 6.9 Hz, ^4J = 1.8 Hz, 1 H, H7a), 2.12–2.31 (m, 1 H, H4), 2.79 (d, ^2J = 13.6 Hz, 1 H, H2), 2.98–3.15 (m, 1 H, H6), 3.23 (dd, ^3J = 12.7 Hz, ^3J = 7.9 Hz, 1 H, H6), 3.45 (d, ^3J = 6.2 Hz, 1 H, H8), 3.73 (d, ^2J = 13.4 Hz, 1 H, H2), 6.05 (s, 1H, H9), 7.25 (dd, ^3J = 9.1 Hz, ^4J = 2.5 Hz, 1 H, H5'), 7.65 (dd, ^3J = 4.4 Hz, ^4J = 0.9 Hz, 1 H, H7'), 7.97 (d, ^3J = 9.0 Hz, 1 H, H3'), 8.05 (dd, ^3J = 2.5 Hz, ^4J = 0.9 Hz, 1 H, H8'), 8.72 (d, ^3J = 4.6 Hz, 1 H, H2')

MS (PI–EI, 70eV): *m/z* = 253 (100) [M – C_4H_9], 310.1 (36) [M]

Optical rotary power:

$[\alpha]_D = -15°$, $[\alpha]_{578} = -15°$, $[\alpha]_{546} = -12°$, $[\alpha]_{436} = 42°$ (c = 1.03, EtOH)

Elemental analysis:	calcd.:	C 73.52	H 7.14	N 9.03
	found:	C 72.74	H 7.16	N 8.85

5.5 Catalysis

5.5.1 The amino acid systems

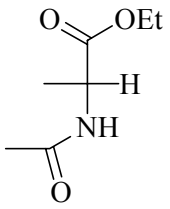
5.5.1.1 General standard procedure

The substrates **1**–**3** (0.74 mmol) were stirred with 10 mol% optically active base in abs. THF (9 mL) under nitrogen for 24 h at 70 °C. Conversion was monitored with TLC (SiO_2 plates) using EtOAc as eluent. Compounds **1**–**6** were made visible heating with molybdatophosphoric acid.

The solvent was removed at room temp. and the residue was dissolved in EtOAc (25 mL). 2 M HCl (15 mL) was added in order to remove the base as the hydrochloride. After extraction with EtOAc (3×25 mL), the organic layer was dried over Na_2SO_4 and evaporated at room temp.

5.5.1.2 Characterisation of the products

5.5.1.2.1 Ethyl *N*-acetylalaninate (4)



$C_7H_{13}NO_3$ (159.2)
Properties: colorless oil

IR (neat): ν [cm^{-1}] = 3280s (br) (N–H); 3060s, 2960s, 2920s (C–H); 1730s (C=O); 1650s (amide I); 1530s (amide II); 1440s, 1360s (C-H)

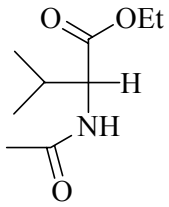
^{1}H NMR (250 MHz, [D_6]DMSO): δ [ppm] = 1.16 (t, ^3J = 7.1 Hz, 3 H, CH_2CH_3), 1.23 (d, ^3J = 7.2 Hz, 3 H, CH_3), 1.82 (s, 3 H, $COCH_3$), 4.06 (q, ^3J = 7.1 Hz, 2 H, CH_2CH_3), 4.19 (dq, ^3J = 7.2 Hz, ^3J = 7.2 Hz, 1 H, CH), 8.24 (br d, ^3J = 7.2 Hz, 1 H, NH)

^{1}H NMR conversion control: $COCH_3$ signal of **1**/**4** δ = 1.86/1.82 ppm

GC conditions: Column Restek Rt-ß DEX cst (30 m length, 0.32 mm i.d.), injector temp. 260 °C, detector temp. 260 °C (flame ionisation), column temp. 115 °C, H_2 pressure 0.7 bar, retention times for enantiomers D/L 10.9/11.7 min.

$[\alpha]_D^{20}$ = – 65.6° (c = 0.55, H_2O)[119] for ethyl *N*-acetyl-L-alaninate

5.5.1.2.2 Ethyl *N*-acetylvalinate (5)



$C_9H_{17}NO_3$ (187.2)
Properties: colorless oil

IR (neat): ν [cm^{-1}] = 3300s (N–H); 3070w, 2960m, 2990w, 2880w (C–H); 1740s (C=O); 1660s (amide I); 1550s (amide II); 1470m, 1380s (C-H)

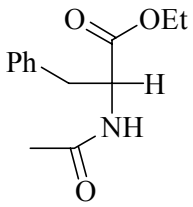
^{1}H NMR (250 MHz, [D_6]DMSO): δ [ppm] = 0.86, 0.87 (2 d, ^3J = 6.7 Hz, 6 H, CH(CH_3)$_2$), 1.17 (t, ^3J = 7.1 Hz, 3 H, CH_2CH_3), 1.86 (s, 3 H, $COCH_3$), 1.99 (oct, ^3J = 6.7 Hz, 1 H, CH(CH_3)$_2$), 3.96–4.22 (m, 3 H, CH_2CH_3, CH), 8.09 (d, ^3J = 7.9 Hz, 1 H, NH)

^{1}H NMR conversion control: $COCH_3$ signal of **2**/**5** δ = 1.89/1.86 ppm

GC conditions: Column Macherey-Nagel Lipodex-E (50 m length, 0.25 mm i.d.), injector temp. 260 °C, detector temp. 260 °C (flame ionisation), column temp. 125 °C, He pressure 2 bar, retention times for enantiomers D/L 25.2/27.0 min.

$[\alpha]_D^{31}$ = – 30.8° (c = 1.00, EtOH)[120] for ethyl *N*-acetyl-L-valinate

5.5.1.2.3 Ethyl *N*-acetylphenylalaninate (6)



$C_{13}H_{17}NO_3$ (235.4)
Properties: colorless solid
Mp: 63–65 °C (lit.[121] 68–69 °C)

IR (neat): ν [cm^{-1}] = 3320s (N–H); 3030w, 2980w, 2940w (C–H); 1740s (C=O); 1650s (amide I); 1540s (amide II); 1450m, 1380m, 1360m (C–H)

^{1}H NMR (250 MHz, [D_6]DMSO): δ [ppm] = 1.08 (t, ^3J = 7.1 Hz, 3 H, CH_2CH_3), 1.78 (s, 3 H, $COCH_3$), 2.86, 2.97 (2 dd, ^2J = 13.6 Hz, ^3J = 8.9 Hz / ^2J = 13.6 Hz, ^3J = 6.1 Hz, 2 H, benzyl H), 4.02 (q, ^3J = 7.1 Hz, 2 H, CH_2CH_3), 4.40 (ddd, ^3J = 7.7 Hz, ^3J = 8.8 Hz, ^3J = 6.1 Hz, 1 H, CH), 7.15–7.32 (m, 5 H, Ph), 8.32 (d, ^3J = 7.9 Hz, 1 H, NH),

^{1}H NMR conversion control: $COCH_3$ signal of **3**/**6** δ = 1.92/1.78 ppm

GC conditions: Column Restek Rt-ß DEX cst (30 m length, 0.32 mm i.d.), injector temp. 260 °C, detector temp. 260 °C (flame ionisation), column temp. 155 °C, He pressure 1.2 bar, retention times for enantiomers D/L 12.0/13.6 min.

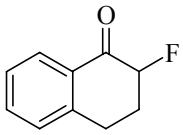
$[\alpha]_D^{23}$ = 87.4° (c = 1.00, $CHCl_3$)[81] for ethyl *N*-acetyl-L-phenylalaninate

5.5.2 The 2-fluoro-1-tetralone (12) system

Benzyl-2-fluoro-1-tetralone-2-carboxylate **11** (50.4 mg, 0.17 mmol) and the chiral base (30 mol%, 0.051 mmol) were dissolved in acetonitrile (10 mL). Then the Pd catalyst (2.5 mol%, 4.25 µmol) was added and the hydrogen atmosphere was provided with gasbags.

After the time given, the reaction mixture was filtered through 10 cm of Celite 545 (washed with CH_2Cl_2) in order to remove the Pd on charcoal. The solvents were evaporated at room temp. In order to remove the base, the residue was filtered through a small SiO_2 column with CH_2Cl_2.

$C_{10}H_9FO$ (164.2)
Properties: slightly yellow oil



IR (neat): ν [cm^{-1}] = 3130w, 2990w, 2900w (C–H); 1730s (C=O); 1630m (C=C); 1510w, 1490w, 1460w (C–H)

^{1}H NMR (300 MHz, $CDCl_3$): δ [ppm] = 2.20–2.38 (m, 1 H, CH_2), 2.53 (dddd, ^3J = 16.8 Hz, ^3J = 10.0 Hz, J = ^{3}5.3 Hz, ^4J = 4.3 Hz, 1 H, CH_2), 3.08 (dd, ^3J = 9.6 Hz, ^3J = 4.1 Hz, 2 H, CH_2), 5.10 (ddd, $^2J_{H,F}$ = 47.9 Hz, ^3J = 12.8 Hz, ^3J = 5.2 Hz, 1 H, FCH), 7.22 (d, ^3J = 7.7 Hz, 1 H, Ph), 7.30 (t, ^3J = 7.5 Hz, 1 H, Ph), 7.48 (td, ^3J = 7.5 Hz, ^4J = 1.4 Hz, 1 H, Ph), 8.01 (dd, ^3J = 8.0 Hz, ^4J = 1.1 Hz, 1 H, Ph)

^{19}F NMR (250 MHz, $CDCl_3$): δ [ppm] = –(191.36–190.25) (m)

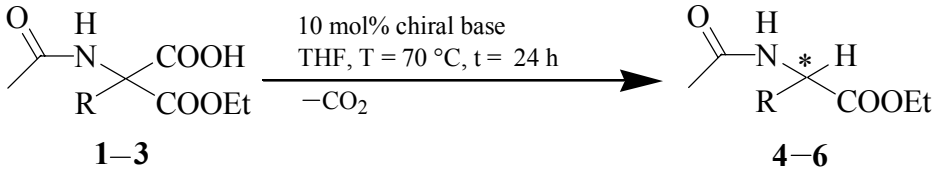
HPLC conditions: Column Chiralcel OD-H, solvent hexane:isopropanol 97:3, flow 0.6 mL/min, T = 25 °C, λ = 210 nm.

Compounds detected: Tracer 2-methoxynaphthalene 12.4 min; 1-tetralone 13.4 min; (*R*)-(+)-2-fluoro-tetralone 22.2 min, (*S*)-(–)-2-fluoro-1-tetralone: 23.5 min; 2-fluoro-1-tetralol: 25.8 min, 28.4 min (*cis-isomers*), 27.6 min, 30.0 min (*trans-isomers*); benzyl 2-fluoro-1-tetralone-2-carboxylate 35.8 and 42.9 min.

$[\alpha]_D^{25}$ = 64.9° (c = 0.43, dioxane)[114] for (*R*)-(+)-2-fluoro-1-tetralone (ee > 95 %)

6 Summary

The enantioselective decarboxylation methodology was applied in order to obtain enantiomerically enriched α-amino acid derivatives. 2-*N*-Acetylamino-2-alkylmalonic acid monoethylesters **1–3** were suitable substrates for this purpose. Various cinchona alkaloid derivatives, mainly benzamide derivatives of 9-amino(9-deoxy)epicinchonine, were screened as catalysts. Full conversion was achieved stirring racemic hemiesters **1**–**3** in THF at 70 °C with 10 mol% of a chiral base for 24 h (Figure 51). The chiral base may be recycled.



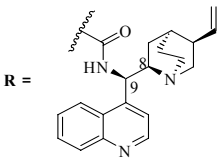
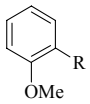
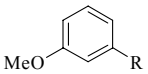
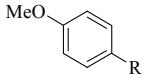
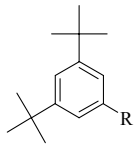
Chiral base (10 mol %): R = 	 **30**	 **32**	 **33**	 **34**	 **35**
Alanine system **1→4** (R = Me): ee [%] of ethyl *N*-acetyl-L-alaninate **4**	48.2; 51.6	16.7; 19.3	52.0; 52.2	49.9; 52.2	58.0; 59.6
Valine system **2→5** (R = $CH(CH_3)_2$): ee [%] of ethyl *N*-acetyl-L-valinate **5**	14.2; 15.6	rac.	9.7; 13.2	11.8; 13.7	48.0
Phenylalanine system **3→6** (R = CH_2Ph): ee [%] of ethyl *N*-acetyl-L-phenylalaninate **6**	65.7; 69.0	37.1; 37.8	63.7; 65.4	69.3; 71.1	65.8; 67.7

Figure 51: *Selected results of the decarboxylation of hemiesters **1–3***

While the commercially available cinchona alkaloids cinchonine, cinchonidine, quinine and quinidine gave poor results in first testings, benzamides of 9-amino(9-deoxy)epicinchonine turned out to be effective catalysts. Independent of the alkyl substituent R of hemiesters **1**–**3**, it was found that with *ortho*-substituted benzamide **32** and also other *ortho*-substituted benzamides enantiomeric excess decreased dramatically. The phenylalanine system **3→6** delivered the best results with up to 70%

ee using *N*-(9-deoxyepicinchonine-9yl)-4-methoxybenzamide **34**. Slightly inferior results were achieved in the alanine system **1→4** obtaining up to 60% ee with base **35**. The valine system **2→5** gave generally worse results, except for catalyst **35**. Besides benzamides of 9-amino(9-deoxy)epicinchonine, the corresponding sulfonamides showed similar results while other derivatives resulted in minor enantiomeric excess.

A kinetic study with the alanine system **1→4** helped to confirm that no kinetic resolution occured in this catalytic reaction, as the enantiomeric excess stayed widely constant.

Another approach in catalytic enantioselective decarboxylation is to start from ß-keto-benzylesters, which are cleaved in the first step by Pd-induced hydrogenolysis. This cascade reaction was investigated starting from benzyl 2-fluoro-1-tetralone-2-carboxylate **11** (Figure 52).

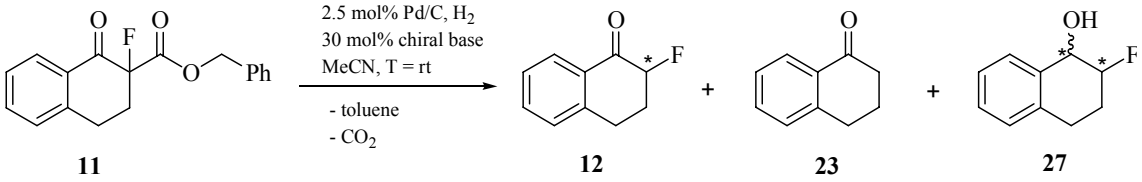


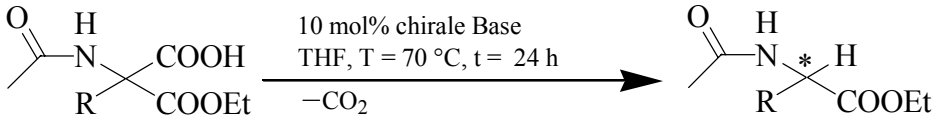
Figure 52: *The 2-fluoro-1-tetralone system*

The type of Pd on charcoal used was crucial. Pd/C type 807104 from Merck delivered reproducible results. Besides the desired product 2-fluoro-1-tetralone **12**, two byproducts appeared, the defluorinated product 1-tetralone **23** and 2-fluoro-1-tetralol **27**.

ß-Aminoalcohols proved to be inappropriate catalysts in this system, as they highly promoted defluoriniation and gave no enantiomeric excess. In contrast to the catalytic decarboxylation leading to α-amino acid derivatives, in the 2-fluoro-1-tetralone **12** system the commercial cinchona alkaloids turned out to be successful catalytically active bases inducing up to 65% ee, while derivatives of them led to clearly decreased optical induction.

7 Zusammenfassung

Die Methode der enantioselektiven Decarboxylierung wurde angewendet, um Enantiomeren-angereicherte α-Aminosäurederivate zu erhalten. 2-*N*-Acetylamino-2-alkylmalonsäure monoethylester **1–3** waren geeignete Substrate hierfür. Verschiedene China-Alkaloidderivate, vor allem Benzamidderivate von 9-Amino(9-deoxy)epicinchonin, wurden als Katalysatoren getestet. Voller Umsatz wurde erreicht durch Rühren der racemischen Hemiester **1**–**3** in THF bei 70 °C mit 10 mol% chiraler Base für 24 h (Abbildung 53). Die chirale Base kann zurückgewonnen werden.



1–3 **4–6**

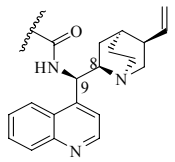
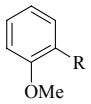
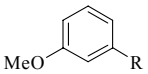
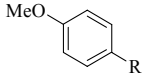
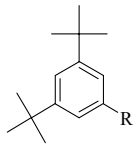
Chirale Base (10 mol %): R = 	 **30**	 **32**	 **33**	 **34**	 **35**
Alanin-System **1→4** (R = Me): ee [%] von *N*-Acetyl-L-alaninethylester **4**	48.2; 51.6	16.7; 19.3	52.0; 52.2	49.9; 52.2	58.0; 59.6
Valin-System **2→5** (R = $CH(CH_3)_2$): ee [%] von *N*-Acetyl-L-valinethylester **5**	14.2; 15.6	rac.	9.7; 13.2	11.8; 13.7	48.0
Phenylalanin-System **3→6** (R = CH_2Ph): ee [%] von *N*-Acetyl-L-phenylalaninethylester **6**	65.7; 69.0	37.1; 37.8	63.7; 65.4	69.3; 71.1	65.8; 67.7

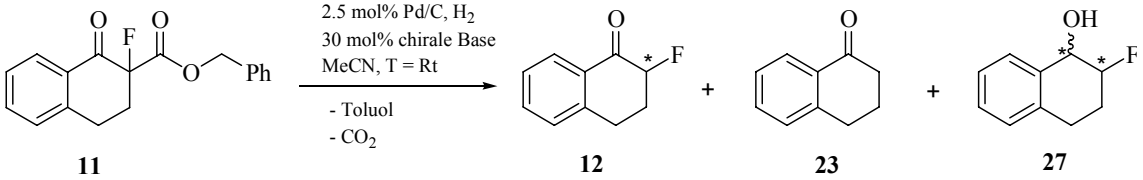
Abbildung 53: *Ausgewählte Ergebnisse der Decarboxylierung von Hemiestern **1–3***

Während die kommerziellen China-Alkaloide Cinchonin, Cinchonidin, Chinin und Chinidin in ersten Tests schlechte Ergebnisse lieferten, erwiesen sich Benzamide von 9-Amino(9-deoxy)epicinchonin als effektive Katalysatoren. Unabhängig vom Alkylsubstituenten R der Hemiester **1–3** zeigte sich, dass das *ortho*-substituierte Benzamid **32** und auch andere *ortho*-substituierte Benzamide den Enantiomerenüberschuss drastisch verringern. Das Phenylalanin-System **3→6** ergab die

besten Ergebnisse von bis zu 70% ee mit *N*-(9-Deoxyepicinchonin-9yl)-4-methoxybenzamid **34**. Geringfügig schlechtere Ergebnisse wurden mit dem Alanin-System **1→4** erreicht. Bis zu 60% ee wurden mit Base **35** erzielt. Das Valin-System **2→5** zeigte generell schlechtere Ergebnisse, außer mit Katalysator **35**. Neben den Benzamiden von Amino(9-deoxy)epicinchonin erzielten die Sulfonamide ähnlich gute Ergebnisse, während andere Derivate zu geringeren Enantiomerenüberschüssen führten.

Eine Reaktionskinetik mit dem Alanin-System **1→4** half zu bestätigen, dass in dieser Katalyse keine kinetische Racematspaltung auftritt, da der Enantiomerenüberschuss während der Reaktion weitgehend konstant blieb.

Eine andere Methode der katalytischen enantioselektiven Decarboxylierung geht aus von ß-Keto-benzylestern, die in einem ersten Schritt durch Pd-induzierte Hydrogenolyse gespalten werden. Diese Kaskadenreaktion wurde untersucht für Benzyl 2-fluor-1-tetralon-2-carboxylat **11** (Abbildung 54).



11 **12** **23** **27**

Abbildung 54: *Das 2-Fluor-1-tetralon-System*

Die Art des Palladiums auf Aktivkohle ist äußerst wichtig. Pd/C Typ 807104 von Merck lieferte reproduzierbare Ergebnisse. Außer dem gewünschten Produkt 2-Fluor-1-tetralon **12** entstanden zwei Nebenprodukte, das defluorierte Produkt 1-Tetralon **23** und 2-Fluor-1-tetralol **27**.

ß-Aminoalkohole erwiesen sich als ungeeignete Katalysatoren in diesem System, da sie die Defluorierung stark begünstigen und keinen Enantiomerenüberschuss erzielen. Im Gegensatz zur katalytischen Decarboxylierung, die zu α-Aminosäuren führt, waren im 2-Fluor-1-tetralon-System **11→12** die kommerziellen China-Alkaloide erfolgreiche katalytisch aktive Basen mit einer optischen Induktion von bis zu 65% ee, während Derivate deutlich verringerte Enantiomerenüberschüsse lieferten.

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