"Enantioselective epoxidation of simple alkenes based upon the concept of pi-interactions-facial recognition"

Antequera Garcia, Gema

Abstract
The aim of our project is to build new catalysts for the asymmetric epoxidation of alkenes using $\pi$-interactions as fundamental factors for the control of the facial selectivity. It was decided to employ cinchona alkaloid derivatives as the basic core of our catalysts. We envisage that the alkene would interact selectively with the aromatic rings of the catalyst to give the corresponding epoxide in good enantiomeric excess. Quinuclidine derived catalysts of simplified structures were synthesized to find the best conditions for the experiments using chiral cinchona derivatives. An important result to be taken into account in the development of the chiral catalysts was the influence of the counterion on the conversion rate. The triflate gave the highest epoxidation rates for trans-$\alpha$-methylstyrene. The use of a mixture MeOH/ DMM/ H2O led to a two fold increase in reaction rate and is recommended to increase the van der Waals interactions between the aromatic rings of the catalyst and th...

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III. Cinchona Alkaloids

III.1. Introduction

The demands on quinine as antimalarial during the period of the Second War, encouraged the scientists to research on developing and producing a synthetic version of the quinidine alkaloids rather than relying on the natural source.\(^1,2\) It was in 1944, that Robert Woodward and William Doering\(^3,4\) were able to synthesize quinine in the laboratory.\(^5\) This accomplishment led to a number of synthetic and patented drugs that were manufactured by several pharmaceutical companies (aprox. 700t/year).

Over the last thirty years, cinchona alkaloids have become increasingly popular in organic chemistry, being used as chiral catalysts, ligands, NMR discriminating agents, and so on. We will try to present in this chapter the most important reactions that can be performed asymmetrically by the use of cinchona alkaloid derivatives.\(^6\)

Cinchona alkaloids, with rotational freedom around the C8-C9 and C4'-C9 bonds, are effective chiral organic catalysts. The most common alkaloids are represented in figure III.1.\(^7\) It is worthy to note that these cinchona alkaloids act as bifunctional catalysts since they present Lewis acidic and Lewis basic sites. Both the tertiary amine and the hydroxyl moiety are able to activate and orient a nucleophile and an electrophile respectively.\(^8,9\)

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8 Kacprak, K.; Grawronski, J. *Synthesis* **2001**, *961*
III.2. Cinchona alkaloids as chiral catalysts

Cinchona alkaloids are versatile catalysts that can be employed principally in four types of reactions: C-C bond formation, C-O bond formation, C-Heteroatom bond formation, and miscellaneous reactions such as desymmetrization, hydrogenation, etc...

III.2.1. Carbon-carbon bond formation

III.2.1.1. Alkylation

The first efficient asymmetric synthesis of indanone 3.1 by direct alkylation of 2.13 was reported by the Merck group in 1984. The use of N-(ρ-(trifluoromethyl)-benzylcinchonidinium bromide 2.14 as PTC for the alkylation of indanone 2.13 gave the desired product with an ee of up to 92%.

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11 See figure II.12 for selectivity explanation
This discovery encouraged O'Donnell and his group to use similar PTC (phase transfer catalyst) in the synthesis of new α-amino acids.\textsuperscript{12,13,14} In 1989, they published a catalytic, enantioselective PTC alkylation of the benzophenone imine 2.1, an activated form of glycine (scheme III.2).\textsuperscript{15} A new stereogenic centre was created using the pseudoenantiomeric catalysts 2.22 or 3.3 (scheme III.3). Only modest ee's were then obtained (≈66%), but the optically pure amino acid could be isolated by subsequent recrystallization of these enantio-enriched products. The second-generation catalysts 3.4 and 3.5 have been prepared by an \textit{in situ} \textit{O}-alkylation of the precursors. The protection of the hydroxy moiety enhanced the enantioselectivity of the reaction leading to ee's of up to 81% ee.\textsuperscript{16}

\textsuperscript{12} Marouka, K.; Ooi, T. \textit{Chem. Rev.} \textbf{2003}, \textit{103}, 3013
\textsuperscript{14} For an explanation for the mechanism and stereoselectivity of this reaction, see: Lygo, B.; Andrews, B. I. \textit{Acc. Chem. Res.} \textbf{2004}, \textit{37}, 518
More recently, a new class of chiral PTCs have been simultaneously developed by Lygo\(^\text{17}\) and Corey\(^\text{18}\) (see scheme III.3). This third-generation catalysts, containing the \(N\)-anthracenylmethyl group, provided a great improvement in the asymmetric induction step (scheme III.2). The reaction is supposed to proceed via an ion pair interaction between the enolate and the quaternary ammonium salt formed. The anthracenyl moiety would block one of the faces of the quinuclidine nitrogen favouring the addition of the electrophile by the less hindered face of the enolate, as it can be observed in figure III.2.

**Scheme III.2**

![Figure III.2](image)

**Table III.1**

<table>
<thead>
<tr>
<th>Entry</th>
<th>R-X</th>
<th>catalyst</th>
<th>Base</th>
<th>ee</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>n-BuBr</td>
<td>3.3</td>
<td>50% aq NaOH</td>
<td>52% (R)</td>
<td>61%</td>
</tr>
<tr>
<td>2</td>
<td>CH(_2)=CHCH(_2)Br</td>
<td>3.3</td>
<td>50% aq NaOH</td>
<td>66% (R)</td>
<td>75%</td>
</tr>
<tr>
<td>3</td>
<td>CH(_2)=CHCH(_2)Br</td>
<td>2.22</td>
<td>50% aq NaOH</td>
<td>62% (S)</td>
<td>78%</td>
</tr>
<tr>
<td>4</td>
<td>PhCH(_2)Br</td>
<td>3.3</td>
<td>50% aq NaOH</td>
<td>66% (R)</td>
<td>75%</td>
</tr>
<tr>
<td>5</td>
<td>PhCH(_2)Br</td>
<td>2.22</td>
<td>50% aq NaOH</td>
<td>64% (S)</td>
<td>85%</td>
</tr>
<tr>
<td>6</td>
<td>PhCH(_2)Br</td>
<td>3.5</td>
<td>CsOH·H(_2)O</td>
<td>99% (S)</td>
<td>73%</td>
</tr>
<tr>
<td>7</td>
<td>EtBr</td>
<td>3.5</td>
<td>CsOH·H(_2)O</td>
<td>98% (S)</td>
<td>82%</td>
</tr>
<tr>
<td>8</td>
<td>PhCH(_2)Br</td>
<td>3.6</td>
<td>50% aq NaOH</td>
<td>91% (S)</td>
<td>68%</td>
</tr>
<tr>
<td>9</td>
<td>PhCH(_2)Br</td>
<td>2.23</td>
<td>50% aq NaOH</td>
<td>86% (R)</td>
<td>73%</td>
</tr>
<tr>
<td>10</td>
<td>CH(_2)=CHCH(_2)Br</td>
<td>2.23</td>
<td>50% aq NaOH</td>
<td>88% (R)</td>
<td>62%</td>
</tr>
<tr>
<td>11</td>
<td>CH(_2)=CHCH(_2)Br</td>
<td>3.6</td>
<td>50% aq NaOH</td>
<td>88% (S)</td>
<td>76%</td>
</tr>
<tr>
<td>12</td>
<td>PhCH(_2)Br</td>
<td>3.7</td>
<td>CsOH·H(_2)O</td>
<td>99% (S)</td>
<td>73%</td>
</tr>
<tr>
<td>13</td>
<td>CH(_3)CH(_2)I</td>
<td>3.7</td>
<td>CsOH·H(_2)O</td>
<td>99% (S)</td>
<td>82%</td>
</tr>
</tbody>
</table>

\(^{17}\) Lygo, B.; Wainwright, P. G. *Tetrahedron Lett.* 1997, 38, 8595

Dimeric and trimeric catalysts derived from cinchonidine have also been developed by Jew\textsuperscript{19} and Nájera\textsuperscript{20,21} in a triphasic system water/ toluene/ CHCl\textsubscript{3} for the catalytic enantioselective alkylation of \textbf{2.1} with different alkyl halides (scheme III.3), affording the \(\alpha\)-alkyl-\(\alpha\)-amino acids in good yields and up to 96\% ee.


 Attempts to carry out the alkylation of 2.1 in an homogenous solvent system, led O'Donnell to use in conjunction with the PTC 2.24, the Schwesinger bases BEMP or BTPP. This homogeneous system led to high enantioselectivities and avoided the problems derived from biphasic systems, such as the efficient control of the stirring and allowed shorten reaction time.22

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Trying to simplify the isolation of the final product, polymer-supported cinchona alkaloid derived ammonium salts have also been used as PTC by different groups, but lower ee were obtained in all cases.\textsuperscript{23,24,25,26}

II.2.1.2. Michael addition

Enantioselective Michael additions of glycine derivative 2.1, was carried out by Corey et al.\textsuperscript{27,28} using catalyst 2.24 or 3.7. The reaction was accomplished under biphasic conditions and led to the adducts with excellent enantioselectivities (scheme III.5, entries 1-3). O’Donnell and his group carried out the same reaction under homogeneous conditions (using Schwesinger bases) and obtained adducts with similar enantioselectivities in the presence of Corey’s catalysts (scheme III-5, entries 4-6). This group also tried to develop the reaction using glycine 2.1 supported on Wang resin, obtaining optically active Michael adducts of up to 82% ee.\textsuperscript{29}

\textsuperscript{23} O’Donnell, M. J.; Delgado, F.; Pottorf, R. S. \textit{Tetrahedron} 1999, 55, 6347
\textsuperscript{24} Chinchilla, R.; Mazón, P.; Nájera, C. \textit{Tetrahedron: Asymmetry} 2000, 11, 3277
\textsuperscript{25} Thierry, B.; Plaquevent, J.-C.; Cahard, D. \textit{Tetrahedron: Asymmetry} 2001, 12, 983
\textsuperscript{26} Danielli, T.; Annunciata, R.; Benaglia, M.; Cinquini, M.; Cozzi, F.; Tocco, G. \textit{Tetrahedron: Asymmetry} 2003, 14, 461
\textsuperscript{27} Corey, E. J.; Noe, M. C.; Xu, F. \textit{Tetrahedron Lett.} 1998, 39, 5347
\textsuperscript{28} Zhang, F.-Y.; Corey, E. J. \textit{Org. Lett.} 2000, 2, 1097
\textsuperscript{29} O’Donnell, M. J.; Delgado, F.; Domínguez, E.; de Blas, J.; Scoot, W. L. \textit{Tetrahedron: Asymmetry} 2001, 12, 821
In 1978, Wynberg reported the first asymmetric Michael addition of nitromethane to chalcone, catalyzed by the chiral quaternary ammonium salt 3.15. Disappointing ees were obtained (only 10% ee).\(^{30}\)

Deng et al. studied the 1,4-addition of dimethyl and diethylmalonate to nitroalkenes, in the presence of different cinchona alkaloids. Excellent levels of enantioselectivities (92-98% ee) were reached with a variety of heteroaryl nitroalkenes.\(^{31}\)

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III. Cinchona Alkaloids

\[ R'\text{NO}_2 + \text{ROOC\text{--COOR}} \rightarrow \text{ROOC\text{--COOR}} \]

Scheme III.7

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R'</th>
<th>Catalyst</th>
<th>T</th>
<th>ee</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>Ph</td>
<td>3.19</td>
<td>-20 °C</td>
<td>93%</td>
<td>98%</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>Ph</td>
<td>3.20</td>
<td>-20 °C</td>
<td>96%</td>
<td>98%</td>
</tr>
<tr>
<td>3</td>
<td>Me</td>
<td>Ph</td>
<td>3.20</td>
<td>-55 °C</td>
<td>99%</td>
<td>93%</td>
</tr>
<tr>
<td>4</td>
<td>Et</td>
<td>Ph</td>
<td>3.19</td>
<td>-20 °C</td>
<td>90%</td>
<td>86%</td>
</tr>
<tr>
<td>5</td>
<td>Me</td>
<td>4-Cl-Ph</td>
<td>3.19</td>
<td>-20 °C</td>
<td>97%</td>
<td>97%</td>
</tr>
<tr>
<td>6</td>
<td>Me</td>
<td>4-MeO-Ph</td>
<td>3.19</td>
<td>-20 °C</td>
<td>97%</td>
<td>90%</td>
</tr>
<tr>
<td>7</td>
<td>Me</td>
<td>2-NO\text{2}-Ph</td>
<td>3.19</td>
<td>-20 °C</td>
<td>97%</td>
<td>90%</td>
</tr>
</tbody>
</table>

Scheme III.8

Catalyst 3.19 was also tested for the addition of the cyclic ketoester 3.22 to nitroalkene 3.16. Very high enantioselectivity and diastereoselectivity was obtained. The reaction was extended to other nitroalkenes with excellent stereocontrol, even when no aromatic substituent was present on the Michael acceptor.\(^{32}\)

\[ \text{Ph\text{--NO}_2 + \text{Et\text{--CO}}_2\text{Et}} \rightarrow \text{Ph\text{--NO}_2} \]

Scheme III.8

The first Michael addition of thiols to cyclic enones catalyzed by cinchona alkaloids was described by Wynberg in 1981.33 A good ee of 93% was obtained in the addition of thiol 3.27 to cyclohexenone 3.28 in the presence of cinchonidine as catalyst.34

Higher enantioselectivities were obtained when 3.29-(DHQD)$_2$PYR was used instead of cinchonidine in the enantioselective addition of thiol 3.27 to a variety of cyclic enones.35
Intramolecular and intermolecular Michael additions/ ring closure have been described by Gaunt and co-workers.\textsuperscript{36,37} Cinchona derivatives 3.29 and 3.33 catalyzed an enantioselective synthesis of functionalised cyclopropanes in high yields and with high ee’s. The mechanism is described in scheme III.12.

\[ \text{NR}_3^*: 3.29 \text{ or } 3.33 \]

Scheme III.12

\[ \text{CsHCO}_3 + \text{CsBr} \]

\[ \text{Cs}_2\text{CO}_3 \]

\[ \text{CsHCO}_3 + \text{CsBr} \]

\[ \text{NR}_3^*: 3.29 \text{ or } 3.33 \]

Scheme III.13

<table>
<thead>
<tr>
<th>Entry</th>
<th>R’</th>
<th>R''</th>
<th>R'''</th>
<th>ee</th>
<th>yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NEt$_2$</td>
<td>Ph</td>
<td>H</td>
<td>97%</td>
<td>94%</td>
</tr>
<tr>
<td>2</td>
<td>O’Bu</td>
<td>OMe</td>
<td>NBoc$_2$</td>
<td>97%</td>
<td>90%</td>
</tr>
</tbody>
</table>


III.2.1.3. Aldol reaction

In 1993, Shibasaki and his group\textsuperscript{38} described the first use of the cinchona alkaloid 3.37 in asymmetric aldol (Henry) reactions. Unfortunately, only moderate yields and low enantioselectivities (up to 23% ee) were obtained.

\[ \text{3.36} + \text{3.38} \rightarrow \text{3.39} \]

41% yield, 23% ee

Scheme III.14

Miller\textsuperscript{39} investigated the catalytic asymmetric synthesis of β-hydroxy-α-amino acids by aldol reaction of the glycine derivative 2.1 with various aldehydes, under PTC conditions, and in the presence of the ammonium salt 2.22. The aldol products were obtained in good yields but with moderate diastereoselectivity. An increase in the chain length of aldehyde 3.40 afforded higher diastereomeric excess, probably due to the increased solubility of the aldehyde in the organic phase, where it displaces the enolate-catalyst complex.

\[ \text{2.1} + \text{3.40} \rightarrow \text{3.41} \]

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>yield</th>
<th>de</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH$_3$</td>
<td>46%</td>
<td>14%</td>
</tr>
<tr>
<td>2</td>
<td>CH$_2$CH$_2$CH$_3$</td>
<td>54%</td>
<td>43%</td>
</tr>
<tr>
<td>3</td>
<td>Ph</td>
<td>92%</td>
<td>0%</td>
</tr>
<tr>
<td>4</td>
<td>CH$_2$CH$_2$Ph</td>
<td>76%</td>
<td>33%</td>
</tr>
</tbody>
</table>

Scheme III.15

High diastereoocontrol (13:1 syn: anti) could be reached when Corey and co-workers\textsuperscript{40} performed the aldol reaction of trimethylsilyl enol ether 3.42 with various aldehydes, in

\textsuperscript{39} Garsparski, C. M.; Miller, M. J. Tetrahedron 1991, 47, 5367
\textsuperscript{40} Horikawa, M.; Busch-Petersen, J.; Corey, E. J. Tetrahedron Lett. 1999, 40, 3843
the presence of catalyst 3.43 (scheme III.16). Shioiri\textsuperscript{41} also studied the aldol reaction of cyclic silyl enol ethers with benzaldehyde in the presence of the cinchonidinium fluoride derivative 3.47. High de’s and ee’s were observed (scheme III.17).

\begin{center}
\begin{tabular}{|c|c|c|c|}
\hline
Entry & \( R \) & yield & \( \text{syn:anti} \) & \( \text{syn ee} \) \\
\hline
1 & \( \text{iPr} \) & 70\% & 6 : 1 & 83\% \\
2 & C\textsubscript{6}H\textsubscript{11} & 81\% & 13 : 1 & 46\% \\
3 & \( n\text{-C}_{6}\text{H}_{13} \) & 79\% & 3:1 & 91\% \\
\hline
\end{tabular}
\end{center}

**Scheme II.16**

\begin{center}
\begin{tabular}{|c|c|c|c|}
\hline
Entry & yield & ee erythro & ee threo \\
\hline
1 & 74\% & 72\% (2R,2’S) & 22\% (2R, 2’R) \\
\hline
\end{tabular}
\end{center}

**Scheme III.17**

\textsuperscript{41} Ando, A.; Miura, T.; Tatematsu, T.; Shioiri, T. *Tetrahedron Lett.* 1993, 34, 1507
III.2.1.4. Morita-Baylis-Hillman reaction

The Morita-Baylis-Hillmann reaction (MBH), reported for the first time in 1968,\(^{42}\) has been widely studied by the groups of Drewes,\(^{43}\) Markó\(^{44}\) and Shi\(^{45}\) but only moderate ee’s have been obtained. Hatakeyama and co-workers have published a highly enantioselective MBH reaction using cinchona derivative 3.51 as the nucleophile. Various aldehydes condensed with the very reactive Michael acceptor HFIPA 3.50 giving high enantiomeric excess. Methyl acrylate was also used, but it gave very low enantioselectivities and when acrylate 3.50 was used as activated alkene, shorter reaction rates were obtained. The hydroxyl group at C-6’ on the catalyst, plays an important role, stabilizing by an intramolecular hydrogen bonding the oxy anion intermediate. The adducts 3.52 were obtained with enantioselectivities of up to 99% ee in moderate yield (31-58% yield). Aromatic aldehydes as well as aliphatic aldehydes can be employed with equal efficiency.\(^{46}\)

\[
\begin{array}{c}
\text{HO} \quad \text{O} \\
\text{CF}_3 \\
\text{CF}_3 \\
\text{N} \\
\text{H} \\
\end{array}
\quad \text{3.51 (10 mol%)}
\quad \begin{array}{c}
\text{HO} \\
\text{O} \\
\text{CF}_3 \\
\text{CF}_3 \\
\end{array}
\quad \begin{array}{c}
\text{OH} \\
\text{O} \\
\text{CF}_3 \\
\text{CF}_3 \\
\text{R} \\
\end{array}
\quad \begin{array}{c}
\text{R} \\
\text{OH} \\
\text{O} \\
\text{CF}_3 \\
\text{CF}_3 \\
\end{array}
\quad \begin{array}{c}
\text{R} \\
\text{R} \\
\text{OH} \\
\text{O} \\
\text{CF}_3 \\
\text{CF}_3 \\
\end{array}
\quad \begin{array}{c}
\text{R} \\
\text{R} \\
\text{OH} \\
\text{O} \\
\text{CF}_3 \\
\text{CF}_3 \\
\end{array}
\quad \begin{array}{c}
\text{R} \\
\text{R} \\
\text{OH} \\
\text{O} \\
\text{CF}_3 \\
\text{CF}_3 \\
\end{array}
\quad \begin{array}{c}
\text{R} \\
\text{R} \\
\text{OH} \\
\text{O} \\
\text{CF}_3 \\
\text{CF}_3 \\
\end{array}
\]

**Scheme III.18**

The mechanism described in scheme III.19 would rationalize the absolute stereochemistry of the products and the important role played by the OH at C6’. Two betaine intermediates can be formed from the reaction of the enolate A with an aldehyde. Both intermediates B and C are stabilized by intramolecular hydrogen bonding between the oxy anion and the phenolic hydroxyl group. Intermediate C suffers from steric interactions between Y and the ester and quinuclidine moieties (see D, X = H, Y = R). This intermediate reacts mainly with a second aldehyde to form the adduct (S)-3.53 as the major product. However, the intermediate B undergoes facile elimination due to lower steric hindrance. In this case, the ester (R)-3.52 is obtained as main product (see D, Y = H, X = R).\(^{46}\)

\(^{43}\) Drewes, S. E.; Freese, S. D.; Emslie, N. D.; Roos, G. H. P. *Synth. Commun.* 1988, 18, 1565
Hatakeyama et al. also studied the aza-Baylis-Hillmann reaction of activated imines with HFIPA 3.50, catalyzed by β-isocupreidine 3.51. The reaction proceeded with a facial selectivity opposite to that observed when aldehydes were used as substrates. The (S)-adducts 3.55 were obtained in up to 67% ee. After recrystallization, enanti-enriched adducts (up to >99 % ee) can be obtained.47

The enantioselectivity observed is determined by steric hindrance at the betaine intermediate level. Enolate A forms two betaine intermediates B and C stabilized by H bond between the phenolic alcohol and the amidate ion. Intermediate C, that suffers a severe steric congestion, would afford the (R)-enantiomer by slow elimination of the catalyst. However, intermediate B gives faster the aza-Baylis-Hillman product, resulting in the (S)-enantiomer as main product.47
III.2.1.5. Diels–Alder reaction

The first enantioselective Diels–Alder reaction, catalyzed by quinidine, was described by Henri B. Kagan and Olivier Riant in 1989.\textsuperscript{48} Anthrone 3.56 reacted with N-methylmaleimide 3.57, in the presence of catalytic amounts of quinidine, at -50 °C, to give the corresponding cycloadduct 3.58 in 61% ee. In the proposed mechanism of the reaction, the anthranone dienolate is suggested to form an ion-pair with the quaternized nitrogen of the catalyst. Meanwhile, the dienophile is hydrogen-bonded through the hydroxyl group of the catalyst (figure III.6).

III.2.1.6. Synthesis of β-Lactones

In 1982, Wynberg published the first highly enantioselective catalytic [2+2] cycloaddition between activated aldehydes and ketenes, in the presence of quinidine. Enantiomeric excesses of up to 98% ee were observed.\textsuperscript{50}


\textsuperscript{50} Wynberg, H.; Staring, E. G. \textit{J. Am. Chem. Soc.} 1982, 104, 166
More than ten years later, Calter reported the dimerization of methylketene with high enantioselectivity (up to 98% ee). The β-lactone 3.67 was obtained using only 1 mol% of quinidine. Due to the volatility and instability of 3.67, the corresponding (R)-primary alcohol generated by reduction with LiAlH₄ was isolated instead.⁵¹

Romo simplified the Wynberg’s method by generating the ketene in situ from acetyl chloride in the presence of quinidine and Hunig’s base (N,N-diisopropylethylamine) (scheme III.26). Mukaiyama’s reagent is used in the reaction for carboxylic acid activation and generation of the ammonium enolate intermediate proposed in the mechanism (scheme III.27). This new protocol provided fused 5 and 6-membered β-lactones with moderate yields but with high enantioselectivities.⁵² Romo thus avoided two principal limitations of Wynberg’s β-lactone synthesis: the need for a ketene generator and the requirement for activated aldehydes.⁵³

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⁵² Cortez, G. S.; Oh, S. H.; Romo, D. Synthesis 2001, 11, 1731
⁵³ Tennyson, R. L.; Romo, D. J. Org. Chem. 2000, 65, 7248
In the proposed mechanism two different reaction pathways are proposed, the ketene B and the acyl ammonium species C. The intermediate B can undergo nucleophilic attack by the catalyst 3.69 to generate the ammonium enolate species D and E. On the other hand, the same intermediates D and E could be generated from C obtained by direct acylation of the quinidine derivative by the activated acid A. Due to ring strain consideration, only the cis-aldolate F could cyclize, eliminating the quaternary ammonium quinidine 3.69 and the cis-β-lactone 3.71.53
III. Cinchona Alkaloids

Scheme III.27
Recently, Nelson\textsuperscript{54} and Calter\textsuperscript{55} have used the trimethylsilyl ethers of quinidine 3.73 and quinine 3.72 for the cycloaddition reaction of ketenes with aldehydes. The corresponding $\beta$-lactones are obtained with ee's of up to 99% and high diastereoselectivities.

\[ \text{R'} \quad \text{O} \quad \text{R''} \]

Scheme III.28

The Lewis acid used in the reaction would activate the aldehyde allowing the ketene/aldehyde addition and avoiding the ketene dimerization. The obtained results proved to be strongly dependent on the size of the Lewis acid used. Small metals such as Li, Y or Eu gave high cis-selectivity. However, bigger metals such as Gd or Sc afforded presumably the trans-isomer. The possible transition states that determine the final stereochemistry are described below. It is believed that the trans-lactone is formed through an open-transition state while the cis-isomer should be by a closed transition state.

\begin{center}
<table>
<thead>
<tr>
<th>Entry</th>
<th>R'</th>
<th>R''</th>
<th>ee %</th>
<th>de %</th>
<th>yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H</td>
<td>CH$_2$OBn</td>
<td>84%</td>
<td>----</td>
<td>70%</td>
</tr>
<tr>
<td>2</td>
<td>Me</td>
<td>CH$_2$C$_2$Ph</td>
<td>&gt;99%</td>
<td>96%</td>
<td>84%</td>
</tr>
<tr>
<td>3</td>
<td>Me</td>
<td>CH$_2$OBn</td>
<td>99%</td>
<td>76%</td>
<td>68%</td>
</tr>
<tr>
<td>4</td>
<td>Me</td>
<td>C$_6$H$_5$</td>
<td>&gt;99%</td>
<td>96%</td>
<td>78%</td>
</tr>
</tbody>
</table>
\end{center}


### II.2.1.7. Synthesis of β-Lactams

There are few methods available for the enantioselective synthesis of β-lactams, but Lectka and co-workers were the first to report the asymmetric [2+2] cycloaddition of *in situ* generated ketenes with *N*-tosylimines, catalyzed by quinine ester 2.19. The desired β-lactams 3.77 were obtained in moderate yields but high ee (up to 99% ee) and cis/ trans ratios up to 99/1 were observed. Addition of 10 mol% of In(OTf)₃ to the reaction mixture afforded comparable selectivity but higher yields (scheme III.30, entry 4). Two main explanations are proposed to explain this increase: (1) The metal could activate only the imine A (figure III.7) or (2) the metal could combine the imine and the enolate forming an activated complex B with the metal.

---


[58] Doyle, M. P.; Kalinin, A. V. *Synlett* 1995, 10, 1075


III.2.1.8. Cyanation

Deng has described the asymmetric addition of cyanide to ketones. This reaction is catalyzed by the cinchona alkaloids acting as chiral Lewis bases. \[ 3.79-(DHQD)\text{PHN} \] and \[ 3.80-(DHQD)_2AQN \] gave the best results, leading to adducts \[ 3.77 \] in up to 97\% ee\(^{61}\). The ion pair is believed to be responsible, in the TS, for the enantioselectivity of the reaction.

---

This methodology has also been extended to the asymmetric cyanosilylation of α,α-dialkoxy ketones. High yields and enantioselectivities were obtained when 3.83-(DHQD)_2PHAL was used as chiral catalyst.\textsuperscript{62}

A new catalyst 3.86 have recently been developed in Corey’s laboratories to carry out the enantioselective Strecker reaction of N-allylbenzaldimines with HCN. This catalyst favours N’-H-N hydrogen bond and π-π-interactions with the substrate in the chiral pocket. These van der Waal forces allow the attack of CN⁻ in an enantioslective way.63

![Scheme III.36](image)

### III.2.1.9. Other additions

Cinchonine also catalyzed the addition of trifluoromethylsilane to aldehydes and ketones to afford trifluoromethyl alcohols with up to 51% ee (scheme III.33).64 Furthermore, enantioselective Horner-Wadsworth-Emmons reactions of a phosphonate with cyclohexanone derivatives leads to alkenes in up to 54% ee (scheme III.34).65 Moreover, in the presence of quinine as catalyst, the asymmetric Ireland-Claisen rearrangement of N-protected glycine allyl esters affords the corresponding γ,δ-unsaturated amino acids in up to 93% ee (scheme III.35).66

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63 Huang, J.; Corey, E. J. Org. Lett. 2004, 6, 5027
III. Cinchona Alkaloids

**Scheme III.33**

\[ R' \text{Me}_3\text{SiCF}_3 \quad 10-20 \text{ mol}\% \quad 3.93 \]

toluene, -78 °C

1. \[ R''O \]
2. \[ \text{aq HCl} \]

<table>
<thead>
<tr>
<th>Entry</th>
<th>R'</th>
<th>R''</th>
<th>yield</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>H</td>
<td>99%</td>
<td>37% (R)</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>Me</td>
<td>91%</td>
<td>48% (R)</td>
</tr>
</tbody>
</table>

**Scheme III.34**

\[ \text{Bu} \quad 3.90 \quad \text{R''OPOOCH}_2\text{R'} \quad 3.91 \]

1. \[ 3.94 (20 \text{ mol}\%) \]
benzene, RbOH

2. \[ \text{HCl/ EtOH, 60 °C} \]

<table>
<thead>
<tr>
<th>Entry</th>
<th>R'</th>
<th>R''</th>
<th>yield</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et</td>
<td>Et</td>
<td>69%</td>
<td>54%</td>
</tr>
</tbody>
</table>

**Scheme III.35**

\[ \text{F}_3\text{C} \quad \text{2.95} \quad \text{R''OPOOCH}_2\text{R'} \quad \text{Al(OiPr)}_3 (1 \text{ eq}) \]

<table>
<thead>
<tr>
<th>Entry</th>
<th>R'</th>
<th>R''</th>
<th>yield</th>
<th>ee</th>
<th>ds</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et</td>
<td>Me</td>
<td>33%</td>
<td>91%</td>
<td>97%</td>
</tr>
<tr>
<td>2</td>
<td>Ph</td>
<td>Me</td>
<td>30%</td>
<td>81%</td>
<td>90%</td>
</tr>
</tbody>
</table>

**Scheme III.37**
III.2.2. Carbon-oxygen bond formation

III.2.2.1. Epoxidation

Since the first example of asymmetric epoxidation of electron-deficient alkenes using benzylated quaternary quinidinium salt 3.47, different cinchona alkaloid derivatives have been tested leading up to 98% ee in the epoxidation of enones.67

![Scheme III.36](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>R'</th>
<th>R''</th>
<th>yield</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ph</td>
<td>Ph</td>
<td>96%</td>
<td>93%</td>
</tr>
<tr>
<td>2</td>
<td>4-MeOC₆H₄</td>
<td>Ph</td>
<td>70%</td>
<td>95%</td>
</tr>
<tr>
<td>3</td>
<td>cyclo-C₆H₁₁</td>
<td>Ph</td>
<td>85%</td>
<td>94%</td>
</tr>
<tr>
<td>4</td>
<td>n-C₆H₁₁</td>
<td>4-FC₆H₄</td>
<td>90%</td>
<td>91%</td>
</tr>
<tr>
<td>5</td>
<td>Ph</td>
<td>4-FC₆H₄</td>
<td>93%</td>
<td>98%</td>
</tr>
<tr>
<td>6</td>
<td>4-NO₂C₆H₄</td>
<td>4-FC₆H₄</td>
<td>97%</td>
<td>95%</td>
</tr>
</tbody>
</table>

III.2.2.2. Asymmetric dihydroxilation

After the first reported asymmetric dihydroxylation (AD) of olefins by Sharpless and Hentges,68 using dihydroquinine acetate or dihydroquinidine acetate, the improvements carried out on this method have transformed it into an efficient system to prepare optically active diols.

The development of the AD reaction involved the extensive variation of the cinchona alkaloids as catalyst. More than 350 cinchona-based ligands were tested in this reaction leading to remarkable enantioselectivities in the case of both functionalized and non-functionalized olefins.69

The process became catalytic in osmium in 1988, when Markó and Sharpless carried out the reaction using cinchona derivatives and N-methylmorpholine N-oxide as co-oxidant.70 The promising ee achieved encouraged the Sharpless’ group to improve the reaction’s conditions, and better enantioselectivities could be reached by the optimisation of the alkaloid ligands, co-oxidants, osmium source and solvent system.71,72,73 From the plethora of ligands developed, catalyst 3.83, 3.29, 3.100 are

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67 For a more detailed study see: Chapter IV.3.2.2. Asymmetric phase transfer catalysts
68 Hentges, S. G.; Sharpless, K. B. J. Am. Chem. Soc. 1980, 102, 4263
69 Markó, I. E.; Svendsen, J. S. Comprehensive Asymmetric Catalysis; Eds. Springer: Berlin, 1999, pp 713
complementary and their use leads to the AD of almost all olefins in high enantiomeric excess. Table III.1 displays some results obtained with the “best” ligands for different types of alkenes.

Table II.1

<table>
<thead>
<tr>
<th>Olefin class</th>
<th>Preferred ligand</th>
<th>Ee range</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PYR</td>
<td>30-97%</td>
</tr>
<tr>
<td></td>
<td>PHAL</td>
<td>70-97%</td>
</tr>
<tr>
<td></td>
<td>IND</td>
<td>20-90%</td>
</tr>
<tr>
<td></td>
<td>PHAL</td>
<td>90-99%</td>
</tr>
<tr>
<td></td>
<td>PHAL</td>
<td>90-99%</td>
</tr>
<tr>
<td></td>
<td>PYR</td>
<td>20-97%</td>
</tr>
</tbody>
</table>

From a close examination of the facial selectivities obtained using various ligands and different olefins, an empirical rule can be derived that enables prediction of the facial selectivity of this process. Typically, the SW quadrant must be occupied by the sterically most-demanding substituent, normally the aromatic group. This rule can be applied to every class of ligand. Only a few exceptions to this rule have been found when terminal alkenes were used as substrates.

Figure III.10

Table III.1 displays some results obtained with the “best” ligands for different types of alkenes.

3.83-(DHQD)₂PHAL
3.29-(DHQD)₂PYR
3.100-(DHQD)₂IND

Alk*= dihydroquinidine

Scheme III.37

74 Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. Chem. Rev. 1994, 94, 2483
Electron-deficient olefins, such as enones, sulphur-containing olefins and trans-alkenylphosphonates are good substrates for the AD, leading to excellent ee’s (>93%).\(^{75,76}\) Electron-rich olefins react better that electron-deficient ones (>99% ee). The high enantioselectivity observed could be attributed to the ability of the cinchona derivatives to form a lipophilic enzyme-like pocket around the metal centre. Van der Waal type interactions may lead to further stabilization of the TS and consequently enable higher rates of reaction and enantioselectivities to be obtained.\(^{76,77,78}\)

Highly efficient cinchona alkaloid-containing polymer supported catalysts have been developed by Song,\(^{79}\) Bolm\(^{80}\) and Janda\(^{81}\) showing reaction rates and enantioselectivities comparable to that of the monomeric catalysts.

**III.2.2.3. Asymmetric aminohydroxylation**

Catalytic asymmetric aminohydroxylation (AA) is a close relative of the AD. The asymmetric conversion of alkenes into N-protected vicinal amino alcohols, published by Sharpless in 1986,\(^{82}\) provided access to the synthesis of a large number of biologically active compounds. The reaction employs as ligands quinidine or dihydroquinidine, linked to a phthalazine or anthraquinone spacer, catalytic amounts of an osmium species, in combination with stoichiometric nitrogen sources, that also functions as the oxidant, to carry out the AA of alkenes.\(^{83}\)

Different nitrogen sources have been studied in the AA of alkenes. The \(N\)-halogenated oxidants can be derived from sulfonamides, carbamates, amides or amino-containing heteroaromatic functions. Chloramine-T \([\text{TsN(Na)Cl}]\) that was initially used has been rapidly superseded by other derivatives (\(p\)-nitrosulfonamide or 2-(trimethylsilyl) ethylsulfonamide) that led to easier deprotection of the amino group and greater enantio- and regioselectivity.\(^{84,85}\)

Carbamates as nitrogen sources are widely applied due to an easier deprotection under mild conditions. Carbamates, with less sterically demanding substituent at the nitrogen atom, gave better results.\(^{86}\)

---

\(^{78}\) For the stabilization of the TS see: Chapter II.3. Cinchona alkaloid examples
\(^{81}\) Han, H.; Janda, K. D. *Tetrahedron Lett.* 1996, 118, 7632
\(^{83}\) For a discussion of the mechanism see: Bodkin, J. A.; McLeod, M. D. *J. Chem. Soc., Perkin Trans, 1* 2002, 2733
A major advance, that simplified the isolation of the final product, is based upon the use of \( N \)-halogenated amides.\(^{87}\) These nitrogen oxidants can be employed successfully with cinnamates, acrylates, styrenes and terminal alkenes.\(^{88}\) In these cases, the reaction gave also better results with less sterically demanding \( N \)-substituents.\(^{89}\)

The observed enantioselectivities and diastereoselectivities, can be predicted by the Sharpless' mnemonic device described before for the AD, through in these cases, they vary with the structure of the alkene used.\(^{83}\) The regioselectivity of the AA is greatly influenced by many factors (alkene polarisation, alkene substitution, etc), but in general, it was observed that the influence of the cinchona alkaloid dominates the regioselectivity.\(^{92}\) Ligands derived from phthalazine or anthraquinone gave complementary regioselectivity and are the most successfull ligands described so far for the AA. The differences in regioselectivity was proposed to arise from different orientation of the substrate with respect to the Os-ligand complex.\(^{93}\)

---

89 Demko, Z. P.; Bartsch, M.; Sharpless, K. B. *Org. Lett.* 2000, 2, 2221
Hergenrother et al. have recently reported a chemo- and regioselective variant of the AA reaction of styrene derivatives based upon the careful control of the pH of the reaction. When the pH of the reaction was maintained between 7.5-8.5, the addition of the nitrogen source occurred at the carbon distal from the aromatic ring, independently of the substitution of the styrene substrate, the solvent or even the ligand used.94

The toxicity and high cost of OsO₄ and cinchona alkaloids have limited the application of the AA on a large scale. In an attempt to make this method more accessible, polymer bound cinchona derivatives have been reported that could be easily recovered and reused. Song95 and Lin96 have developed immobilized cinchona derived ligands for the AA of cinnamate derivatives. The solid-phase method allows the catalysts to be reused more than five times without significant decrease of the ee. Up to 99% ee have been obtained.

In general, the most important limitation of the AA, apart from the deprotection of the amine group,97 is the prediction of the regioselectivity of the final product that depends on many factors (solvent, alkene, ligand…).
### III.2.3. Other carbon-heteroatom bond formation

#### III.2.3.1. C-N: aziridines, 2H-azirines, amination

Aires-de-Sousa and co-workers reported in 1996 a catalytic enantioselective aziridination of α,β-unsaturated esters by N-acyl-N-arylhydroxylamines 3.117. Aziridine 3.119 was obtained in 61% ee in the presence of catalyst 3.116, but in only 12% yield.\(^9\)

![Scheme III.42](image)

Further studies were carried out by this group in order to improve these results, alas without success.\(^9\) In contrast, Tardella and co-workers,\(^1\) employing 2-(phenylsulfanyl)-2-cycloalkenone 3.120 were able to obtain the chiral aziridine 3.121, in 93% yield and 75% ee when catalysts 2.23 or 3.116 were used.

![Scheme III.43](image)

Chiral 2\(H\)-azirines were also prepared from 3.122\(^1\) or 3.123\(^1\) by treatment with quinidine, dihydroquinidine or quinine. The azirines 3.124 or 3.125 were obtained in moderate to good enantioselectivities.

---

\(^{9}\) Aires-de-Sousa, J.; Lobo, A. M.; Prabhakar, S. *Tetrahedron Lett.* 1996, 37, 3183

\(^{9}\) Aires-de-Sousa, J.; Prabhakar, S.; Lobo, A. M.; Rosa, A. M.; Gomes, M. J. S.; Corvo, M. C.; Williams, D. J.; White, A. J. P. *Tetrahedron: Asymmetry* 2004, 15, 3349

\(^{1}\) Fioravanti, S.; Mascia, M. G.; Pellacani, L.; Tardella, P. A. *Tetrahedron* 2004, 60, 8073


\(^{1}\) Palacios, F.; Ochoa de Retama, A. M.; Gil, J. I. *Tetrahedron Lett.* 2000, 41, 5363
Catalytic enantioselective $\alpha$-amination of $\beta$-ketoesters and $\beta$-keto lactones has recently been reported by the group of Pihko. The $\alpha$-amination of 3.126 and 3.128, with dibenzyl azodicarboxylate 3.130, catalyzed by cinchonine, afforded the corresponding products 3.127 and 3.129 in up to 90% ee and 64% ee respectively.

Deng and co-workers used the modified cinchona alkaloid 3.132 (and its pseudoenantiomer) to catalyse the amination of $\alpha$-cyanooesters bearing an aryl substituent. The adducts 3.134 have been obtained in good yields and with excellent enantioselectivities (up to 99%).

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103 Pihko, P. M.; Pohjakkallio, A. Synlett 2004, 12, 2115
IIII.2.3.2. C-S: chiral sulfinates, chiral sulfoxides

The initial procedure of Mikolajczyc\textsuperscript{105} describing the enantioselective sulfination of alcohols with \(p\)-toluenesulfinyl chloride, in the presence of quinine, gave only moderate enantioselectivities. However recent investigations have provided the sulfinate adducts with higher ee’s. Shibata\textsuperscript{106} has published the asymmetric sulfination reaction of alcohols, catalysed by 3.69-9-acetoxyquinidine (or 9-acetoxyquinine). This alkaloid reacts with the sulfinyl chloride to form a complex that acts as an asymmetric sulfinating agent of achiral alcohols. The corresponding arenesulfinate 3.136 could be isolated with up to 95% ee.

Ellman and co-workers\textsuperscript{107} have used the commercially available quinidine to perform a catalytic enantioselective sulfinyl transfer reaction. Other chiral amines such as (-)-sparteine, only provided low conversions and poor enantiomeric excess. However, when quinidine was used, they obtained the sulfinate esters 3.138 with up to 90% ee and 92% isolated yield.

\textsuperscript{105} Drabowicz, J.; Lagedz, S.; Mikolajczyc, M. Tetrahedron 1988, 44, 5243
\textsuperscript{107} Peltier, H. M.; Evans, J. W.; Ellman, J. A. Org. Lett. 2005, 7, 1733
The asymmetric oxidation of sulfides has been carried out by Sudalai and Thakur\textsuperscript{108} using an heterogeneous catalytic system (WO\textsubscript{3}-30% H\textsubscript{2}O\textsubscript{2}) in the presence of 3.20-(DHQD)\textsubscript{2}PYR. Sulfoxides, possessing up to 90% ee have been obtained by this method, but only low to moderate yields were observed. Recently, Senanayake \textit{et al.}\textsuperscript{109} have improved the enantioselectivity and the yield of this process. Chiral \textit{t}-butylsulfinate (Rs)-3.139 was formed as precursor of 3.140, by reacting quinidine, thionyl chloride and \textit{t}-butylmagnesium chloride. Sulfinate 3.139 was then treated with phenylmagnesium chloride to give (R)-\textit{t}-Butylphenyl sulfoxide in 93% isolated yield and >99% ee.

\begin{equation}
\text{SOCl}_2 + \text{Et}_3\text{N} \rightarrow \text{PhMgCl} \rightarrow \text{BuMgCl}
\end{equation}

\textbf{Scheme III.50}

\section{III.2.3.3. C-X: C-Cl, C-F}

Catalytic enantioselective chlorination/ esterification have been developed by Lectka and co-workers.\textsuperscript{110,111} The process generates \textit{\alpha}-chloroesters 3.142 from acid halides using commercially available benzoylquinine and polychloroquinone. High enantioselectivities and moderate to good yields were obtained. This transformation is believed to occur via the generated ketene, which reacts with the chiral quinine.
derivative. The enolate formed reacts with the halogen source in a tandem halogenation/esterification sequence.

Scheme III.51

Enantioselective fluorination of α-substituted esters, α-substituted nitriles, and silyl enol ethers has been developed independently by Cahard\textsuperscript{112} and Shibata\textsuperscript{113}. Both research teams used different cinchona alkaloid derivatives and Selectfluor as the fluorinating agent. The corresponding products were obtained in moderate to good enantioselectivities.


### III.2.4. Miscellaneous

#### III.2.4.1. Heterogeneous hydrogenation

The first heterogeneous asymmetric hydrogenation was carried out by Orito\textsuperscript{114} in 1978 using α-keto esters in the presence of cinchonidine or 9-MeO-cinchonidine. The catalytic system involved an achiral activator responsible for the reduction (Pt), a chiral promotor, responsible for the enantioselectivity (cinchona alkaloid) and a support (Al\textsubscript{2}O\textsubscript{3}). The groups of Blaser\textsuperscript{115,116} and Sun\textsuperscript{117} have studied this reaction in order to improve the enantioselectivity. They used different cinchona alkaloids and varied the

\textsuperscript{116} Blaser, H. U.; Jallet, W. L.; Müller, M.; Studer, M. \textit{Catalysis Today} \textbf{1997}, 37, 441
\textsuperscript{117} LeBlond, C.; Liu, W. J.; Sun, Y.-K. \textit{J. Am. Chem. Soc.} \textbf{1999}, 121, 4920
reaction’s conditions. By carrying out the reaction in benzene as solvent, the reduction of 3.155 provides the (S)-α-hydroxy ester 3.156 in up to 95% ee.

\[
\begin{align*}
&\text{CO}_2\text{Et} \\
&\text{O} \\
&\text{CO}_2\text{Et} \\
&\text{Pt/ Al}_2\text{O}_3, \text{H}_2, 70 \text{ bar, rt} \\
&\text{benzene} \\
&\text{cinchonine} \\
&\text{3.155} \\
&\rightarrow \\
&\text{OH} \\
&\text{O} \\
&\text{CO}_2\text{Et} \\
&\text{3.156} \\
&\text{ee up to 95%}
\end{align*}
\]

Scheme II.53

Other functionalised keto derivatives have been assayed in this enantioselective hydrogenation using Pt/ Al₂O₃ and cinchonidine or 9-MeO-cinchonidine as chiral additives. High enantioselectivities and high yields were generally observed in all cases. Some representative examples are displayed in scheme III.56.¹¹⁸,¹¹⁹,¹²⁰

\[
\begin{align*}
&\text{O} \\
&\text{N} \\
&\text{CH}_2\text{CF}_3 \\
&\text{3.157} \\
&\text{Pt/ Al}_2\text{O}_3, \text{H}_2, 60 \text{ bar, rt} \\
&\text{AcOH} \\
&\text{cinchonidine} \\
&\rightarrow \\
&\text{OH} \\
&\text{N} \\
&\text{CH}_2\text{CF}_3 \\
&\text{3.158} \\
&\text{up to 58% ee}
\end{align*}
\]

\[
\begin{align*}
&\text{O} \\
&\text{O} \\
&\text{Me} \\
&\text{3.159} \\
&\text{Pt/ Al}_2\text{O}_3, \text{H}_2, 70 \text{ bar, rt} \\
&\text{toluene} \\
&9\text{-O-methyl dihydrocinchonidine} \\
&\rightarrow \\
&\text{OH} \\
&\text{O} \\
&\text{O} \\
&\text{3.160} \\
&\text{up to 97% ee}
\end{align*}
\]

\[
\begin{align*}
&\text{F}_3\text{C} \\
&\text{O} \\
&\text{O} \\
&\text{3.161} \\
&\text{Pt/ Al}_2\text{O}_3, \text{H}_2, 70 \text{ bar, rt} \\
&\text{toluene} \\
&\text{cinchonidine} \\
&\rightarrow \\
&\text{OH} \\
&\text{F}_3\text{C} \\
&\text{3.162} \\
&\text{up to 92% ee} \\
&\text{99% chemoselectivity}
\end{align*}
\]

\[
\begin{align*}
&\text{Ph} \\
&\text{CO}_2\text{Et} \\
&\text{3.163} \\
&\text{Pt/ Al}_2\text{O}_3, \text{H}_2, 5.8 \text{ bar, rt} \\
&\text{AcOH} \\
&\text{dihydrocinchonidine} \\
&\rightarrow \\
&\text{Ph} \\
&\text{OH} \\
&\text{CO}_2\text{Et} \\
&\text{3.164} \\
&\text{up to 91% ee}
\end{align*}
\]

Scheme III.54

Methylpyruvate was enantioselectively hydrogenated using a polymer supported iridium catalyst, instead of Pt on alumina, in the presence of 9-MeO-cinchonidine. A high ee of 98% was obtained.¹²¹

¹¹⁸ Wang, G.-Z.; Mallat, T.; Baiker, A. Tetrahedron: Asymmetry 1997, 8, 2133
¹²¹ Zuo, X.; Liu, H.; Yue, C. J. Mol. Cat. A: Chem. 1999, 147, 63
III.2.4.2. Homogeneous reduction

Moderate to low enantioselectivities have been reached during the reduction of ketones and \( \alpha,\beta \)-unsaturated ketones with LiAlH\(_4\), in the presence of cinchona alkaloids. Reduction with NaBH\(_4\) did not lead to better results. Only a modest ee of 32% has been reported so far.\(^{122,123}\)

III.2.4.3. Decarboxylation

The enantioselective decarboxylation of \( \alpha \)-aminomalonates was found to be an interesting way to allow the synthesis of \( \alpha \)-amino acids, but the use of quinidine as catalyst only led to moderate enantioselectivities (up to 52% ee).\(^{124}\) The only good result described in the literature involves the use of epicinchonine \(3.165\) in the decarboxylation of naproxen nitrile \(3.166\), that occurs in 72% ee.\(^{125}\)

![Scheme III. 55](image)

III.2.4.3. Desymmetrization

The first attempt to carry out the desymmetrization of prochiral and meso cyclic anhydrides, catalyzed by epiquinidine (0.1 eq) was reported by Oda in 1987.\(^{126}\) Only moderate enantioselectivities were obtained then, but this result prompted many other groups to improve the enantioselectivity of the ring-opening process. Aitken increased the ee by using catalytic amounts of cinchonidine or quinidine as catalysts in the reaction of tetracyclic anhydrides with methanol. Functionalised chiral products were obtained in up to 97% yield and 52% ee (93% after recrystallization).\(^{127}\)

The best results in this field have been recently reported by Bolm et al.\textsuperscript{128} who obtained up to 99% ee and 99% yield in the opening of prochiral anhydrides 3.171 by methanol, even though stoichiometric amounts of quinine or quinidine were required. Deng\textsuperscript{129} also carried out an effective catalytic desymmetrization using 5 mol% of (DHQD)$_2$AQN or (DHQ)$_2$AQN. He obtained up to 98% ee (93% yield) in the ring opening of the cyclic anhydride 3.171 (scheme II.52). As it is shown below, desymmetrization of prochiral and \textit{meso} anhydrides can be predicted.

A new phosphinite derivative of cinchonine was developed by Fujimoto to carry out the desymmetrization of \textit{meso}-diols. Good yields and high ee’s were obtained for the corresponding monobenzoylated diol. The cinchona catalyst 3.175 plays a double role, since it contains a Lewis basic phosphorus centre and a tertiary amine group. The first one would activate the acylating reagent, while the tertiary amine would be transformed into the corresponding quaternary ammonium salt by trapping a proton during the stereoselective desymmetrization process.\textsuperscript{130}

\begin{footnotesize}
\begin{itemize}
\item \textsuperscript{128} Bolm, C.; Schiffer, I.; Atodiresei, I.; Hackenberger, C. P. R. \textit{Tetrahedron: Asymmetry} \textbf{2003}, 14, 3455
\item \textsuperscript{129} Chen, Y.; Tian, S.-K.; Deng, L. \textit{J. Am. Chem. Soc.} \textbf{2000}, 122, 9542
\item \textsuperscript{130} Mizuta, S.; Sadamori, M.; Fujimoto, T.; Yamamoto, I. \textit{Angew. Int. Ed. Engl.} \textbf{2003}, 42, 3383
\end{itemize}
\end{footnotesize}
Alcoholysis using supported cinchona alkaloid derivatives as catalysts afforded chiral hemiesters in moderate conversion but high ee (up to 92% ee).\textsuperscript{131,132}

### III.2.4.4. Kinetic resolution

Deng extended his anhydride opening methodology to parallel kinetic resolution of racemic monosubstituted anhydrides. The reaction of racemic 2-substituted succinic anhydrides with an alcohol was carried out in the presence of \textit{3.80}-(DHQD)\textsubscript{2}AQN (10 mol\%).\textsuperscript{133}

\begin{center}
\begin{tabular}{|c|c|c|c|}
\hline
Entry & R & yield & ee \\
\hline
1 & Ph & 99\% & 82\%  \\
2 & Me & 99\% & 86\%  \\
3 & -(CH\textsubscript{2})\textsubscript{4} & 85\% & 94\%  \\
\hline
\end{tabular}
\end{center}

\textsuperscript{131} Song, Y.-M.; Choi, J. S.; Yang, J. W.; Han, H. *Tetrahedron Lett.* 2004, 45, 3301
\textsuperscript{132} Kim, H. S.; Song, Y.-M.; Choi, J. S.; Yang, J. W.; Han, H. *Tetrahedron* 2004, 60, 12051
III. Cinchona Alkaloids

1,3-Dioxolane-2,4-diones are also good substrates for the parallel KR. (DHQD)$_2$AQN is used as catalyst for the enantioselective ring opening by the alcohol. This ligand also acts as a Lewis base and takes also part in the \textit{in situ} racemization of the 1,3-dioxolane-2,4-diones by abstraction of the acidic α-proton of \ref{3.181}. Efficient dynamic KR was achieved for a variety of 5-substituted-1,3-dioxolane-2,4-diones \ref{3.181}, affording the ester $R$-$\ref{3.182}$ in 90-96% ee and 65-85% isolated yield.\textsuperscript{134}

\[
\begin{array}{c|c|c|c|c|c|c}
\text{Entry} & \text{R OH} & T \degree C & \text{conv (\%)} & \text{3.179/3.180} & \% ee \text{ 3.179} & \% ee \text{ 3.180} \\
1 & \text{MeOH} & 25 & 100 & 39/61 & 74 & 67 \\
2 & \text{EtOH} & 25 & 100 & 49/51 & 82 & 67 \\
3 & \text{CF$_3$CH$_2$OH} & 25 & 100 & 49/51 & 81 & 72 \\
4 & \text{CF$_3$CH$_2$OH} & -25 & 100 & 44/56 & 91 & 80 \\
\end{array}
\]

Scheme III.59

Deng’s group also demonstrated the synthetic utility of the cinchona alkaloid catalyzed resolution by showing its ability to generate optically active α-amino acids by opening of their urethane derivatives. When methanol was used in the reaction, enantioselectivities between 67% to 94% ee were obtained, depending upon the

\[
\begin{array}{c|c|c|c|c}
\text{Entry} & R' & R''OH & \text{yield} & \text{ee (R)} \\
1 & \text{Ph} & \text{EtOH} & 71\% & 95\% \\
2 & 4-Cl-C$_6$H$_4$ & \text{EtOH} & 70\% & 96\% \\
3 & \text{PhCH$_2$} & \text{EtOH} & 46\% & 93\% \\
4 & (CH$_3$)$_2$CH & \text{Allyl} & 48\% & 90\% \\
\end{array}
\]

Scheme III.60

\textsuperscript{134} Tang, L.; Deng, L. \textit{J. Am. Chem. Soc.} \textbf{2002}, 124, 2870
substituent $R'$ and the protecting group $P$. However, only moderate to low yields were observed. Improvements on the ee were observed when the reaction was carried out at room temperature in the presence of an allylic alcohol. The corresponding amino ester $R$-$3.185$ was obtained in 89-95% ee and 86-95% yield from racemic urethane-protected $\alpha$-amino acid $N$-carboxyanhydride $3.184$. The complex formed in the reaction between the amine and the alcohol mediated by H bond is supposed to determine the enantioselectivity of the final product.

![Diagram of the reaction](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>$R'$</th>
<th>ROH</th>
<th>$P$</th>
<th>$T$ °C</th>
<th>ee $R$-$3.185$</th>
<th>yield $R$-$3.185$</th>
<th>conv.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhCH$_2$</td>
<td>allylic alcohol</td>
<td>Cbz</td>
<td>23</td>
<td>91%</td>
<td>97%</td>
<td>100%</td>
</tr>
<tr>
<td>2</td>
<td>PhCH$_2$</td>
<td>allylic alcohol</td>
<td>Fmoc</td>
<td>23</td>
<td>90%</td>
<td>98%</td>
<td>100%</td>
</tr>
<tr>
<td>3</td>
<td>PhCH$_2$</td>
<td>MeOH</td>
<td>Cbz</td>
<td>-60</td>
<td>93%</td>
<td>48%</td>
<td>51%</td>
</tr>
<tr>
<td>4</td>
<td>PhCH$_2$</td>
<td>MeOH</td>
<td>Fmoc</td>
<td>-78</td>
<td>92%</td>
<td>50%</td>
<td>51%</td>
</tr>
<tr>
<td>5</td>
<td>PhCH$_2$</td>
<td>MeOH</td>
<td>Boc</td>
<td>-40</td>
<td>67%</td>
<td>56%</td>
<td>59%</td>
</tr>
<tr>
<td>6</td>
<td>Allylic alcohol</td>
<td>Cbz</td>
<td>-30</td>
<td>92%</td>
<td>93%</td>
<td>100%</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Allylic alcohol</td>
<td>Cbz</td>
<td>23</td>
<td>89%</td>
<td>86%</td>
<td>100%</td>
<td></td>
</tr>
</tbody>
</table>

Scheme III.61

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136 Hang, J.; Deng, L. *Synlett* 2003, 12, 1927