Asymmetric hydrogenation of imines, enaminines and N-heterocycles using phosphoramidite ligands
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In this chapter the asymmetric hydrogenation of N-aryl β-enamino acid esters is described. Full conversions and enantioselectivities of up to 70% were obtained using an iridium catalyst with a mixture of the phosphoramidite ligand PipPhos and an achiral phosphine.
6.1 Introduction

6.1.1 Asymmetric hydrogenation of enamines

The synthesis of optically active amines is of considerable interest due to the presence of these motifs in natural products and in other molecules which show interesting biological activities. One of the approaches in the synthesis of chiral amines is the asymmetric hydrogenation of imines or enamines (Figure 6.1). Chiral cyclic tertiary amines are essential structural units in natural products and drugs.

![Figure 6.1 Model substrates for the hydrogenation of enamines](image)

Pioneering work on the enantioselective catalytic hydrogenation of simple enamines was done by Buchwald et al. using a chiral titanocene catalyst (Scheme 6.1).

**Scheme 6.1** The first asymmetric hydrogenation of enamines

Buchwald et al., 1994
With 5 mol% of catalyst and up to 5 bar of hydrogen pressure, excellent enantioselectivities and high yields were obtained. However, the use of expensive phenylsilane is a disadvantage of this method.

In 2000, Börner et al. reported the first rhodium-catalyzed hydrogenation of enamines with up to 72% ee, using a bisphosphine ligand.6

Most of the current examples in the hydrogenation approaches require an acyl protecting and chelating group on the nitrogen of the unsaturated β-amino acids or enamines in order to achieve high reactivity and enantioselectivity.3,7,8 A major drawback of these approaches are additional steps of introducing and removing the acyl protecting group, which limits their application.9 In addition, to obtain high enantioselectivity, this method typically requires prior separation of the (Z)- and (E)-N-acyl enamine isomers, as most synthetic approaches to these precursors are poorly selective.

Figure 6.2 Representative monodentate ligands reported for the asymmetric hydrogenation of simple enamines and N-acyl enamines
Chapter 6

Developing new catalysts that allow the asymmetric hydrogenation of simple enamines and N-acyl enamines is still in great demand, due to the fact that suitable catalytic systems are scarce and substrate scope is rather limited. In recent years, however, a rapid development has taken place.\textsuperscript{5,10-15} Figure 6.2 shows the most efficient monodentate ligands reported for the asymmetric hydrogenation of simple enamines and N-acyl enamines. In 2004 Reetz \textit{et al.} reported the use of a mixed ligand approach in the asymmetric hydrogenation of N-acyl enamines. With the use of a rhodium catalyst and a mixture of BINOL-derived phosphites, phosphonites and phosphines up to 97\% ee was obtained.\textsuperscript{15}

In our group, a library of ligands was tested in the rhodium catalyzed asymmetric hydrogenation of N-acyldehydroamino acid esters, acyclic and cyclic N-acyl enamines.\textsuperscript{13} It was found that use of the simple monodentate ligands PipPhos and MorphPhos led to excellent ee's and conversions. Ding also reported the use of a Rh/monodentate phosphoramidite catalytic system in the hydrogenation of both N-acetyl enamines and \(\alpha\)-dehydroamino acids with excellent ee's.\textsuperscript{14}

The asymmetric hydrogenation of cyclic N,N-dialkyl enamines provides a direct approach to the synthesis of optically active cyclic tertiary amines. Since the acyl protecting group on the nitrogen of the unsaturated \(\beta\)-amino acids is often needed as a chelating group, the chiral catalysts that proved to be successful in the asymmetric hydrogenation of enamides can not be simply applied in the asymmetric hydrogenation of N,N-dialkyl enamines. The group of Zhou reported the highly efficient Rh(I)-catalyzed asymmetric hydrogenation of cyclic enamines\textsuperscript{11} and N,N-dialkyl enamines\textsuperscript{12} using monodentate spiro phosphonite ligands, in which the addition of iodine and acetic acid was shown to be crucial for excellent activity and selectivity. Recently, Zhou \textit{et al.} reported the use of iridium catalyzed hydrogenation of exocyclic enamines, with bisphosphine MeO-BIPHEP and iodine as additive. They also described applications to the synthesis of optically active alkaloid (S)-Cusparein and the key intermediate for the synthesis of NMDA-glycine antagonists.\textsuperscript{10}
6.1.2 Asymmetric hydrogenation of \(\beta\)-dehydroamino acids

![Chemical structures of Biologically active compounds with \(\beta\)-amino acid units](image)

**Figure 6.3** Biologically active compounds with \(\beta\)-amino acid units

Enantiomerically pure \(\beta\)-amino acids and their derivatives not only exhibit broad biological activity but are also the building blocks for the synthesis of \(\beta\)-peptides, \(\beta\)-lactam antibiotics and other chiral pharmaceuticals (Figure 6.3).\(^{16}\) Peptides containing \(\beta\)-amino acids show high stability towards enzymatic hydrolysis and are being valuated as promising pharmaceutical products. In addition, \(\beta\)-peptides show interesting three-dimensional structures,\(^{17}\) and they have played an important role in advancing the understanding of enzyme mechanisms, protein conformations, and properties related to molecular recognition.
Therefore the asymmetric synthesis of β-amino acids attracts significant attention.\textsuperscript{18,19}

Figure 6.3 shows some examples of pharmaceutically interesting structures containing a β-aryl-substituted β-amino acid as a common structural component.\textsuperscript{20,21} Taxol is a cancer chemotherapeutic agent, Jasplakinolide exhibits anthelminthic (drugs that expel parasitic worms), insecticidal, and antifungal properties and Elarobifan is an integrin antagonist.

The cyclization of β-amino acids leads to the important family of the β-lactams. The beta-lactam ring is part of the structure of several antibiotic families, principally the penicillins, cephalosporins, carbapenems and monobactams (Figure 6.4).

Figure 6.4 β-lactam antibiotics

Methods for the preparation of optically enriched β-amino acids are predominantly based on stoichiometric reactions with chiral auxiliary agents and to a clearly smaller extent on stereoselective catalytic reactions.\textsuperscript{19,21,22} The most important approach to β-amino acids is from the chiral pool, in particular through the Arndt-Eistert homologation of α-amino acids. One of the most promising methodologies, also regarding industrial application, is the asymmetric hydrogenation of the appropriate β-dehydroamino acid precursors catalyzed by homogeneous Rh or Ru.
Synthesis of N-aryl β-amino acid derivatives via asymmetric hydrogenation

complexes containing chiral phosphane ligands.23 Whereas the asymmetric hydrogenation of α-dehydroamino acids is a standard method with many industrial applications,24 the hydrogenation of β-dehydroamino acids is still an underdeveloped area, mainly because the catalytic behaviour is highly dependent on the structure of the substrate (E or Z isomers, aliphatic or aromatic side chains). Although some results on the asymmetric hydrogenation of β-dehydroamino acid derivatives were published before,7,25 the breakthrough was made by Zhang et al. (Scheme 6.2).26 Using bisphosphine BICP and Duphos ligands, β-amino acid esters were prepared with excellent enantioselectivities and yields. While BICP leads to excellent results in the hydrogenation of (E)-isomer, Duphos is the ligand of choice for both (E) and (Z) β-enamino acid derivatives.

\[
\begin{align*}
\text{(E)} & : \text{R}^1\text{OOC} & \text{or} & \text{COOR}^1 \\
\text{(Z)} & : \text{COOR}^1 \\
\text{rt, H}_2 & \text{Rh precursor, L}^* \\
\text{up to 97% ee} & \text{up to 99% ee}
\end{align*}
\]

**Scheme 6.2** Zhang’s asymmetric hydrogenation of β-dehydroamino acids

While the hydrogenation of acylated enamines is well known, it was quite unexpected that unprotected substrates are amenable to the asymmetric hydrogenation with high ee’s as well. Merck27 and Takasago28 reported independently asymmetric Rh-Josiphos and Ru-BINAP (and analogues) catalyzed hydrogenation of unprotected enamines leading to β-amino acid derivatives. With both catalysts high enantioselectivities were achieved, although the rate is somewhat lower than the hydrogenation of the acylated precursors.

Merck has developed a process for the asymmetric hydrogenation of 1, which is an intermediate in the synthesis of Sitagliptin, an oral
antihyperglycemic drug of the dipeptidyl peptidase-4 (DPP-4) inhibitor class (Scheme 6.3).\textsuperscript{29} Employing a rhodium catalyst with Josiphos as ligand, 1 was hydrogenated with 98\% ee on a \( >50 \) kg scale, although with low to medium TONs and TOFs.

Scheme 6.3 Hydrogenation of the \( \beta \)-dehydroamino acid amide intermediate for Sitagliptin

Figure 6.5 shows the most efficient ligands/catalysts employed in the asymmetric hydrogenation of \( \beta \)-dehydroamino acid derivatives.\textsuperscript{27,30-34} Zhang reported the first highly enantioselective hydrogenation of \( \beta \)-aryl-substituted \( \beta \)-N-acetyl enamino esters, using a ruthenium catalyst with the phosphinite BINAPO ligand.\textsuperscript{33} Excellent enantioselectivities were obtained even though the substrates were used as mixture of (E) and (Z) isomers. Subsequently, the same group reported the use of rhodium/Tangphos catalysts in the asymmetric hydrogenation of \( N \)-aryl \( \beta \)-enamino esters with excellent ee’s.\textsuperscript{30} In our group, \( \beta \)-dehydroamino acid derivatives were hydrogenated with the use of a Rh/phosphoramidite catalysts with excellent ee’s.\textsuperscript{34} Imamoto reported in 2002 the use of unsymmetrical bis(phosphane) ligands in the rhodium catalyzed hydrogenation of \( \alpha \)- and \( \beta \)-dehydroamino acid derivatives and enamides, with up to 72\% ee in the hydrogenation of \( \beta \)-dehydroamino acid derivatives.\textsuperscript{32}
Synthesis of $N$-aryl $\beta$-amino acid derivatives via asymmetric hydrogenation

$$\text{Rh} \text{P} \text{P} \text{R}_2 \text{R}_3$$
$$\text{Me} \text{R}_1$$

up to 72% ee

Imamoto et al., 2002

$$\text{BF}_4^-$$

$$\text{OPAr}_2$$

up to >99% ee

Minnaard, Feringa, de Vries et al., 2002

$$\text{OPAr}_2$$

up to 99% ee

Zhang et al., 2002

$$\text{R} = \text{Ph, Ar = Ph}$$

$$\text{R} = 3,5-\text{Me}_2\text{C}_6\text{H}_3, \text{Ar = Ph}$$

$$\text{R} = \text{Ph, Ar = 3,5-\text{Me}_2\text{C}_6\text{H}_3}$$

$$\text{Zhang et al., 2006}$$

$$\text{PPh}_2$$

up to 96% ee

Lee et al., 2004

$$\text{Me-BDPMI}$$

up to >97% ee

TAKASAGO, 2005

$$\text{BINAP}$$

up to 96% ee

Zhang et al., 2006

$$\text{BINAPO}$$

up to 94% ee

Gladiali, Beller et al., 2007

Figure 6.5 Ligands/catalyst reported for the asymmetric hydrogenation of $\beta$-dehydroamino acid precursors

Lee described the asymmetric synthesis of cyclic $\beta$-amino acid derivatives (homoproline derivatives) via asymmetric hydrogenation, using a rhodium catalysts with chiral bisphosphine ligands.31

The groups of Gladiali and Beller have shown that monodentate chiral BINOL-derived phosphene ligands can be used for various rhodium- and ruthenium-catalyzed hydrogenations. Their application towards the synthesis of $\beta$-amino acid derivatives is shown, and enantioselectivities up to 94% ee were achieved.35

$N$-Aryl $\beta$-amino acid derivatives are key structural elements of many natural products and drug intermediates.36 One of the ways to prepare such compounds is to perform asymmetric hydrogenation of $N$-aryl $\beta$-enamino esters. For example, the most efficient way to introduce a phenyl group on the drugs CGP-68730A or LG-121104 is the enantioselective hydrogenation of a $N$-aryl $\beta$-enamine. Other approaches include the
coupling of an amine and a phenyl moiety, however, the route via asymmetric hydrogenation is more direct (Scheme 6.4).

![Scheme 6.4](image)

Scheme 6.4 Drug candidates with N-aryl amino acid units and potential enamine substrates for the hydrogenation

6.2 Goal of the research

As mentioned earlier, asymmetric hydrogenation of β-enamino acid derivatives represents a direct approach to β-amino acids. In our group phosphoramidite ligands were successfully used in the asymmetric hydrogenation of α- and β-dehydroamino acids with excellent enantioselectivity. We have also shown that iridium with phosphoramidite ligands gives excellent results in the hydrogenation of N-aryl imines (Chapter 4). The goal of this research was to develop an efficient catalyst for the hydrogenation of N-aryl β-enamino esters, as precursors for the synthesis of pharmaceuticals. Therefore, we studied different classes of ligands and different metals in the hydrogenation of N-aryl β-enamino esters.
6.3 Substrate synthesis

A family of enamino esters was prepared from β-keto esters and aniline derivatives.30,38 Only one isomer of the enamines was obtained. Two methods for their synthesis were employed. The β-alkyl N-aryl enamino esters were prepared by stirring of the β-keto ester with aniline in the presence of acetic acid, in an ultrasonic bath (Scheme 6.7, method A). β-Aryl N-aryl enamino esters were prepared by refluxing of the β-keto esters with aniline (or an aniline derivative) in the presence of p-toluenesulfonic acid in ethanol (Scheme 6.5, method B).

**Method A**

\[ \text{Method A} \]

\[ \text{HOAc} \]

\[ \text{ultrasonic bath, 3h} \]

1. \( R = \text{Me}, 60\% \text{ yield} \)
2. \( R = \text{Et}, 76\% \text{ yield} \)

**Method B**

\[ \text{Method B} \]

\[ p-\text{TsOH, EtOH} \]

\[ \text{reflux overnight} \]

3. \( R = \text{H}, 44\% \text{ yield} \)
4. \( R = \text{o-OMe}, 31\% \text{ yield} \)
5. \( R = \text{p-OMe}, 31\% \text{ yield} \)

Scheme 6.5 Synthesis of enamines

6.4 Results

Inspired by the results of the Merck group27 in the asymmetric hydrogenation of unprotected enamines leading to β-amino acid derivatives, we decided to test two ferrocenyl ligands in the rhodium catalyzed hydrogenation of five different N-aryl β-enamino esters.
The reactions were performed using 5 mol% of rhodium precursor and 5 mol% of the ligand, at 5 bar of hydrogen pressure and room temperature, in trifluoroethanol (TFE). High throughput methodology was used for the first set of experiments (see chapter 2 about HTE). Since in the HTE experiment 96 reactions are performed in a single run of the autoclave, reaction mixtures were analyzed after the hydrogenation without purification. Catalysts and ligands used, as well as substrates and additives were dispensed as stock solutions, using a robot. Hydrogenation was performed in a Premex 96-Multi Reactor. The results of the high throughput experiments are presented in Tables 6.1 - 6.5.

Although the role of TFE in hydrogenation reactions has not been completely clarified yet, there have been several reports in which fluorinated alcohols were shown to have a positive effect on the selectivity and rate of the transition metal-promoted reactions, including hydrogenation. It has been reported that the dramatic improvement of enantioselectivity and conversion was obtained in the asymmetric hydrogenation of imines and ketones when trifluoroethanol was used as a solvent. The role of fluorinated alcohols is rationalized as a stabilizer of the active catalyst (as a weakly coordinating ligand), or as a hydrogen bond donor. Therefore, we decided to perform the initial hydrogenation experiments of enamino esters in trifluoroethanol. Results obtained with ferrocenyl ligands are presented in Table 6.1. At 5 bar of hydrogen pressure, high conversions were obtained for all tested substrates with Taniaphos as a ligand (Entries 2, 4, 6, 8, 10). In the case of anisidine substituted enamino esters 4 and 5 conversions were high with both Josiphos and Taniaphos (Entries 7-10). However, determination of the enantiomeric excess of 4a and 5a was unsuccessful both on HPLC or GC.

The highest enantioselectivity was obtained in the hydrogenation of β-phenyl N-phenyl enamino ester 3, using Taniaphos (73% ee, Entry 6). The same ligand induced only 3% ee in the hydrogenation of β-methyl N-phenyl enamino ester 2. On the contrary, good enantioselectivity was obtained for enamines 1 and 2 using Josiphos (51% and 63% ee, respectively, Entries 1, 3).
Synthesis of N-aryl β-amino acid derivatives via asymmetric hydrogenation

Table 6.1 Asymmetric hydrogenation of N-aryl β-enamino esters

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Ligand</th>
<th>Conv. (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>Josiphos</td>
<td>53</td>
<td>51</td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td>Taniaphos</td>
<td>100</td>
<td>nd</td>
</tr>
<tr>
<td>3</td>
<td>2a</td>
<td>Josiphos</td>
<td>68</td>
<td>63</td>
</tr>
<tr>
<td>4</td>
<td>2a</td>
<td>Taniaphos</td>
<td>100</td>
<td>3</td>
</tr>
<tr>
<td>5</td>
<td>3a</td>
<td>Josiphos</td>
<td>50</td>
<td>30</td>
</tr>
<tr>
<td>6</td>
<td>3a</td>
<td>Taniaphos</td>
<td>91</td>
<td>73</td>
</tr>
<tr>
<td>7</td>
<td>4a</td>
<td>Josiphos</td>
<td>86</td>
<td>nd</td>
</tr>
<tr>
<td>8</td>
<td>4a</td>
<td>Taniaphos</td>
<td>99</td>
<td>nd</td>
</tr>
<tr>
<td>9</td>
<td>5a</td>
<td>Josiphos</td>
<td>85</td>
<td>nd</td>
</tr>
<tr>
<td>10</td>
<td>5a</td>
<td>Taniaphos</td>
<td>76</td>
<td>nd</td>
</tr>
</tbody>
</table>

*Reaction conditions: 100 µmol enamino ester, 5 µmol [Rh(COD)2]BF4, 5 µmol L*, 2.55 mL of TFE, rt, 5 bar H2, 16h. *Conversion was determined by GC. *Enantiomeric excess was determined by HPLC. *Enantiomeric excess was not determined due to the overlapping of the peak of an impurity with the peak of the product.

In addition, we examined iridium and ruthenium catalysts in the asymmetric hydrogenation of β-enamino esters (Figure 6.6, Table 6.2). Two cationic iridium catalysts with bidentate P,N-bidentate ligands and a ruthenium catalyst with a phosphoramidite ligand and a chiral diamine were used. Since this ruthenium catalyst gives excellent results in the
hydrogenation of ketones and $\beta$-keto esters,\textsuperscript{42} we decided to study its performance also in the hydrogenation of enamino esters. Using QUINAP as ligand good to excellent conversions were obtained, while the highest ee obtained was in the hydrogenation of 3 (21% ee, Entry 7).

**Table 6.2 Ligands/catalysts employed in the asymmetric hydrogenation of $N$-aryl $\beta$-enamino esters\textsuperscript{a}**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Catalyst</th>
<th>Conv.\textsuperscript{b} (%)</th>
<th>ee\textsuperscript{c} (%)</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>Ir/QUINAP</td>
<td>37</td>
<td>nd\textsuperscript{d}</td>
</tr>
<tr>
<td>2</td>
<td>1a</td>
<td>Ir/Pfaltz</td>
<td>3</td>
<td>nd</td>
</tr>
<tr>
<td>3</td>
<td>1a</td>
<td>Ru Cat A</td>
<td>0\textsuperscript{e}</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>2a</td>
<td>Ir/QUINAP</td>
<td>26</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>2a</td>
<td>Ir/Pfaltz</td>
<td>2</td>
<td>nd</td>
</tr>
<tr>
<td>6</td>
<td>2a</td>
<td>Ru Cat A</td>
<td>0\textsuperscript{e}</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>3a</td>
<td>Ir/QUINAP</td>
<td>69</td>
<td>21</td>
</tr>
<tr>
<td>8</td>
<td>3a</td>
<td>Ir/Pfaltz</td>
<td>53</td>
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<td>4a</td>
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<td>46</td>
<td>nd</td>
</tr>
<tr>
<td>11</td>
<td>4a</td>
<td>Ir/Pfaltz</td>
<td>30</td>
<td>nd</td>
</tr>
<tr>
<td>12</td>
<td>4a</td>
<td>Ru Cat A</td>
<td>0\textsuperscript{e}</td>
<td>-</td>
</tr>
<tr>
<td>13</td>
<td>5a</td>
<td>Ir/QUINAP</td>
<td>94</td>
<td>nd</td>
</tr>
<tr>
<td>14</td>
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<tr>
<td>15</td>
<td>5a</td>
<td>Ru Cat A</td>
<td>0\textsuperscript{e}</td>
<td>-</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Reaction conditions: 100 $\mu$mol enamino ester, 5 $\mu$mol catalyst, 2.55 mL of TFE, rt, 5 bar H\textsubscript{2}, 16h. \textsuperscript{b}Conversion was determined by GC. \textsuperscript{c}Enantiomeric excess was determined by HPLC. \textsuperscript{d}Enantiomeric excess was not determined due to the overlapping of the peak of an impurity with the peak of the product. \textsuperscript{e}Reaction performed in i-PrOH.
Use of the Pfaltz’ oxazolidine ligand resulted in poor conversion in the Ir-catalyzed hydrogenation of β-alkyl N-phenyl β-enamino esters (1, 2, Entries 2 and 5), whereas in the case of β-aryl N-phenyl β-enamino esters up to 89% conversion was observed (Entries 8, 11, 14). The highest ee was obtained in the hydrogenation of substrate β-phenyl N-phenyl β-enamino ester 3 (53% conversion, 46% ee, Entry 8). Ruthenium catalyst A gave no conversion in the hydrogenation of any of the substrates (Entries 3, 6, 9, 12, 15).

**Figure 6.6** Catalysts employed in the asymmetric hydrogenation of N-aryl β-enamino esters

As shown by the Merck group, results of the deuterium labelling studies showed that the hydrogenation of unprotected β-dehydroamino acid derivatives proceeds through the imine tautomer, making the reaction mechanistically analogue to β-ketoester and -amide hydrogenations. As mentioned earlier, since the [Ir(COD)]_2BARF/PipPhos L1 catalyst gave excellent results in the hydrogenation of N-aryl imines, quinolines and quinoxalines, we examined the possibility to use the same catalytic system in the hydrogenation of β-enamino esters. This hydrogenation was
performed using 5 mol% of iridium precursor and 10 mol% of (S)-PipPhos L1 ligand, at 5 bar of hydrogen pressure and room temperature, in dichloromethane. The results are presented in Table 6.3.

**Table 6.3** Asymmetric hydrogenation of N-aryl β-enamino esters using [Ir(COD)₂]BArF/(S)-PipPhos L₁

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Conv. b (%)</th>
<th>ee c (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>21</td>
<td>20</td>
</tr>
<tr>
<td>2</td>
<td>2a</td>
<td>13</td>
<td>36</td>
</tr>
<tr>
<td>3</td>
<td>3a</td>
<td>46</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>4a</td>
<td>37</td>
<td>nd</td>
</tr>
<tr>
<td>5</td>
<td>5a</td>
<td>89</td>
<td>nd</td>
</tr>
</tbody>
</table>

*Reaction conditions: 100 µmol enamino ester, 5 µmol [Ir(COD)₂]BArF, 10 µmol (S)-PipPhos, 2.55 mL of solvent, CH₂Cl₂, 5 bar H₂, 16h. Conversion was determined by GC. Enantiomeric excess was determined by HPLC.*

All substrates tested except enamino ester 5, were hardly converted at 5 bar of hydrogen pressure and room temperature. Substrate 5 was hydrogenated with 89% conversion. In general low enantioselectivities were obtained. The highest ee was obtained in the hydrogenation of β-methyl N-phenyl enamino ester 2, however, with low conversion (13% conversion, 36% ee, Entry 2).

Since reactions with Ir/PipPhos L1 at 5 bar of hydrogen pressure gave low conversions and ee’s, the following experiments were performed at 25 bar of pressure. Various solvents as well as additives were screened in the asymmetric hydrogenation of β-methyl N-phenyl enamino ester 2, β-phenyl
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N-phenyl enamino ester 3 and cyclic enamine 6. The results are presented in Table 6.4.

When reactions were performed in dichloromethane and 25 bar of pressure, results for the hydrogenation of β-enamino esters 2 and 3 were comparable to the experiments performed at 5 bar (Entries 1, 8).

A wide variety of Lewis acid catalysts have been developed on the basis of the Lewis acid-base complexes in organic polar solvents. Lewis acids are among the most useful reagents in reactions with ketones as substrates. We wanted to examine if the addition of the Lewis acid would promote the oxidative addition of the enamine substrate to the iridium. When 5 mol% of Lewis acid (indium bromide) was added to the hydrogenation of 2, the conversion increased from 45% to 68% however, the enantioselectivity dropped from 25 to 12% (Entry 2). In the case of the substrate 3, the conversion dropped significantly by the addition of indium bromide (Entry 9). Using toluene as a solvent, conversions in the hydrogenation of 2 and 3 were somewhat higher, however, the ee stayed low (16 and 17% ee, respectively). In i-propanol, both substrates were hydrogenated with low ee (Entries 4, 11 and 18).

As described in Chapter 4, it is well known that the addition of the Brönsted acid often increases the enantioselectivity or rate of the asymmetric hydrogenation. When 5 mol% of salicylic acid was added to the reaction mixture in the hydrogenation of 2 and 3 in i-propanol the enantioselectivity of 2a increased from 5% to 33%, while for the product 3a an insignificant drop of ee occurred (Entries 5, 12). The explanation of the positive effect of the addition of organic acid on the enantioselectivity may be that the acid protonates the product of the hydrogenation and in this way prevents its coordination to the metal center, and in this way preventing the “catalyst poisoning”.

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Table 6.4 Solvents and additives screening using Ir/PipPhos L1

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Solvent</th>
<th>Additive</th>
<th>Conv. (%)</th>
<th>ee (%)</th>
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<tbody>
<tr>
<td>1</td>
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<td>20</td>
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*aReaction conditions: 100 µmol substrate, 5 µmol [Ir(COD)2]BArF, 10 µmol PipPhos L1, 2.55 mL of solvent, rt, 25 bar H2, 16h. bConversion was determined by GC. cEnantiomeric excess was determined by HPLC. dEnantiomeric excess was determined by GC analysis.
When the reaction was performed in tetrahydrofuran, no ee was observed for product 2a while product 3a was hydrogenated with 73% conversion and 20% ee (Entries 6 and 13).

Adding 10 mol% of iodine as additive in THF, gave racemic products 2a and 3a (Entries 7 and 14). In the case of the hydrogenation of cyclic enamine 6, full conversion was obtained in all solvents and with all additives, however, the highest ee was obtained in the reaction in which iodine was added (20% ee, Entry 21).

We decided to examine the possibility to use a mixtures of phosphoramidites with achiral P-ligands or amines (see Chapter 2). Reactions were performed using 5 mol% of [Ir(COD)2]BARF and (S)-PipPhos L1 as a ligand, at 25 bar of hydrogen pressure and room temperature. When achiral phosphine was used as a second ligand, the ratio between PipPhos L1 and achiral ligand was 2/1. In the reactions where an amine was used as the second ligand, the ratio of ligands was PipPhos L1/amine = 1/1, as in the case of Crabtree’s catalyst. The results of the hydrogenation of substrates 2, 3 and 6 are presented in Table 6.5.

In the case of the addition of the amine ligand, an excellent conversion, but no enantioselectivity was observed with any of the substrates, both when (S,S)-2-Phenyl-1-(1-phenyl-ethyl)-propylamine or triethylamine were added (Entries 2, 3, 7, 8, 12 and 13). When achiral phosphines were added in combination with (chiral) PipPhos, the highest ee was achieved using triphenylphosphine in the hydrogenation of both 2 and 3 (up to 65% ee, Entries 4 and 9). In the case of substrate 3, the conversion was somewhat lower (54%, Entry 9). Substrate 6 was again hydrogenated with excellent conversion however almost racemic product was isolated in all cases (Entries 11-15).
Table 6.5 Asymmetric hydrogenation of enamines using Ir catalysts with mixed ligands

![Chemical structures and reaction conditions](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Achiral ligand</th>
<th>Ir/L*/L</th>
<th>Conv. (%)</th>
<th>ee (%)</th>
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<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>-</td>
<td>1/2/0</td>
<td>45</td>
<td>25</td>
</tr>
<tr>
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<td>Et</td>
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<td>0</td>
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<tr>
<td>3</td>
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<td>Ph$_3$N</td>
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<td>PPh$_3$</td>
<td>1/2/1</td>
<td>100</td>
<td>65</td>
</tr>
<tr>
<td>5</td>
<td>Tri-o-tolylphosphine</td>
<td>1/2/1</td>
<td>48</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>-</td>
<td>-</td>
<td>1/2/0</td>
<td>34</td>
<td>20</td>
</tr>
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<td>3a</td>
<td>Ph$_3$N</td>
<td>1/1/1</td>
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<td>0</td>
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<td>PPh$_3$</td>
<td>PPh$_3$</td>
<td>1/2/1</td>
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<td>45</td>
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<td>Tri-o-tolylphosphine</td>
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<td>5</td>
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<tr>
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<td>-</td>
<td>1/2/0</td>
<td>100</td>
<td>6</td>
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<td>15</td>
<td>Tri-o-tolylphosphine</td>
<td>1/2/1</td>
<td>100</td>
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</tbody>
</table>

$^a$Reaction conditions: 100 µmol substrate, 5 µmol [Ir(COD)$_2$]BArF, 10 µmol (S)-PipPhos L$_1$, 2.55 mL of CH$_2$Cl$_2$ rt, 25 bar H$_2$, 16h. $^b$Conversion was determined by GC. $^c$Enantiomeric excess was determined by HPLC. $^d$Enantiomeric excess was determined by GC analysis.
Synthesis of N-aryl β-amino acid derivatives via asymmetric hydrogenation

Since the PipPhos/triphenylphosphine mixture induced the highest enantioselectivity in the hydrogenation of N-aryl β-enamino esters, we decided to perform this reaction at higher concentration (1 mmol scale, 4 mL of solvent) and lower catalyst loading, on model substrate 1. Various achiral P-ligands were tested in combination with PipPhos L1 (Figure 6.7). Results are depicted in Table 6.6. Reactions were performed at 25 bar of hydrogen pressure and room temperature, using 1 mol% of [Ir(COD)2]BArF, 2 mol% of PipPhos L1 and 1 mol% of achiral ligand, in dichloromethane. The best result was again obtained using triphenylphosphine in combination with PipPhos L1, providing full conversion and 70% ee (Entry 1). With the use of tri-o-tolylphosphine L3 no conversion was obtained, while use of other phosphines having a substituent in the ortho-position also led to low conversions (L5 and L7, Entries 4 and 6).

Table 6.6 Achiral ligands screened in the asymmetric hydrogenation of 1

<table>
<thead>
<tr>
<th>Entry</th>
<th>Achiral ligand</th>
<th>Conv. (%)</th>
<th>ee (%)</th>
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<tr>
<td>2</td>
<td>L3</td>
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<tr>
<td>3</td>
<td>L4</td>
<td>100</td>
<td>52</td>
</tr>
<tr>
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<td>L5</td>
<td>5</td>
<td>-</td>
</tr>
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<td>5</td>
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<td>29</td>
<td>42</td>
</tr>
<tr>
<td>7</td>
<td>L8</td>
<td>6</td>
<td>nd</td>
</tr>
<tr>
<td>8</td>
<td>L9</td>
<td>100</td>
<td>47</td>
</tr>
<tr>
<td>9</td>
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<td>42</td>
<td>40</td>
</tr>
<tr>
<td>10</td>
<td>L11</td>
<td>26</td>
<td>38</td>
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</tbody>
</table>

*Reaction conditions: 1 mmol 1, 0.01 mmol [Ir(COD)2]BArF, 0.02 mmol (S)-PipPhos L1, 0.01 mmol achiral ligand, 4 mL of toluene, 60 °C, 70 bar H2, 20h. *Conversion was determined by 1H NMR. *Enantiomeric excess was determined by HPLC.
Chapter 6

The sterically bulky phosphine L8 caused low conversion (6%, Entry 7). Full conversions and ee’s up to 63% were achieved using phosphines with substituents in the meta or para positions (Entries 3 and 5).

This result suggests that o-substituted achiral phosphines as well as the sterically bulky phosphine L8 are perhaps sterically too demanding for coordination to the iridium together with the PipPhos L1 ligand.

![Achiral P-ligands screened in the asymmetric hydrogenation of 1](image)

*Figure 6.7 Achiral P-ligands screened in the asymmetric hydrogenation of 1*

When trimethylphosphite L9 was used with PipPhos L1, full conversion was accomplished, whereas with addition of triphenylphosphine oxide L10 and HMPA L11 only up to 42% conversion and 40% ee was achieved (Entries 8-10).
Synthesis of N-aryl β-amino acid derivatives via asymmetric hydrogenation

Table 6.7 Ligand screening in the asymmetric hydrogenation of 1

<table>
<thead>
<tr>
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<th>PPh$_3$</th>
<th>Conv. (%)</th>
<th>ee (%)</th>
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<td>2</td>
<td>L12</td>
<td>+</td>
<td>7</td>
<td>nd</td>
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<tr>
<td>3</td>
<td>L13</td>
<td>-</td>
<td>4</td>
<td>nd</td>
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<tr>
<td>8</td>
<td>L15</td>
<td>+</td>
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<td>6</td>
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*Reaction conditions: 1 mmol 1, 0.01 mmol [Ir(COD)$_2$]BArF, 0.02 mmol L*, 4 mL of DCM, rt, 25 bar H$_2$, 16h. Conversion was determined by $^1$H NMR. Enantiomeric excess was determined by HPLC.

Apart from the screening of various achiral ligands, we screened four different phosphoramidite ligands in combination with triphenylphosphine L2 in the hydrogenation of 1. The reactions were performed using 1 mol%
of iridium precursor, 2 mol% of phosphoramidite ligand and 1 mol% of triphenylphosphine, at 25 bar of hydrogen pressure and room temperature, in dichloromethane. Results are presented in Table 6.7.

Phosphoramidite ligands L12 and L13 are derived from different backbones; one has a H8-BINOL and another the 3,3'-substituted BINOL backbone. Ligands L14 and L15 are derived from chiral 2-phenyl-1-(1-phenyl-ethyl)-propylamine with different configurations. Unfortunately all the ligands employed induced disappointingly low conversions. The highest enantioselectivity, however, accompanied by very low conversion was obtained using phosphoramidite L13 in combination with triphenylphosphine (Entry 4, 8% conversion, 46% ee).

We decided to perform the reaction at higher concentration (1 mmol scale, 4 mL of solvent) and lower catalyst loading (1 mol%), on model substrate 1, for the rhodium/ferrocene-based bisphosphine, as well as the rhodium/PipPhos L1 catalytic system. Various solvents were used, and the results are presented in Table 6.8.

The experiment with Josiphos in dichloromethane, led to a similar result as in the HTE experiment with the use of 5 mol% of the catalyst and higher dilution (49% conversion, 48% ee, Entry 1). Also a similar result was obtained in trifluoroethanol (64% conversion, 52% ee, Entry 2). In ethyl acetate a somewhat lower conversion and ee was obtained (30% conversion, 28% ee, Entry 4). In the case of PipPhos L1 no conversion was achieved in dichloromethane and trifluoroethanol, while in ethyl acetate 27% conversion and 20% ee was observed (Entry 8). Very low conversions were obtained in toluene, in the case of both Josiphos and PipPhos L1 (3% and 6%, respectively, Entries 3 and 7).
Synthesis of N-aryl β-amino acid derivatives via asymmetric hydrogenation

Table 6.8 Asymmetric hydrogenation of 1 using Josiphos and PipPhos L1 ligands\textsuperscript{a,b}

<table>
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<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Ligand</th>
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<td>2</td>
<td>CF\textsubscript{3}CH\textsubscript{2}OH</td>
<td>Josiphos</td>
</tr>
<tr>
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<td>Toluene</td>
<td>Josiphos</td>
</tr>
<tr>
<td>4</td>
<td>EtOAc</td>
<td>Josiphos</td>
</tr>
<tr>
<td>5</td>
<td>DCM</td>
<td>PipPhos</td>
</tr>
<tr>
<td>6</td>
<td>CF\textsubscript{3}CH\textsubscript{2}OH</td>
<td>PipPhos</td>
</tr>
<tr>
<td>7</td>
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<td>PipPhos</td>
</tr>
<tr>
<td>8</td>
<td>EtOAc</td>
<td>PipPhos</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Reaction conditions: 1 mmol 1, 0.01 mmol [Rh(COD)\textsubscript{2}]BF\textsubscript{4}, 0.01 mmol Josiphos, 4 mL of solvent, rt, 25 bar H\textsubscript{2}, 16h. \textsuperscript{b}1 mmol 1, 0.01 mmol [Rh(COD)\textsubscript{2}]BF\textsubscript{4}, 0.02 mmol (S)-PipPhos, 4 mL of solvent, rt, 25 bar H\textsubscript{2}, 16h. *Conversion was determined by \textsuperscript{1}H NMR. Enantiomeric excess was determined by HPLC.

6.5 Conclusion

In conclusion, we examined various catalytic systems in the hydrogenation of β-dehydroamino acid derivatives. The highest enantioselectivity was obtained using an iridium catalyst with a mixture of the phosphoramidite ligand PipPhos L1 and triphenylphosphine L2 (full conversion, 70% ee). As shown previously in the literature, rhodium catalysts with ferrocene-based bisphosphine ligands led to excellent results in the hydrogenation of unprotected β-dehydroamino acid derivatives.\textsuperscript{27} In our case, Josiphos and Taniaphos ligands induced good conversions and ee’s in the hydrogenation of N-aryl β-amino acid derivatives. Phosphoramidites are interesting from the point of view of industrial application, due to their low cost, easy preparation and excellent performance in the asymmetric hydrogenation.\textsuperscript{49} Therefore, in the view of future results, a broad screening of both chiral phosphoramidites and
achiral ligands should be performed. It would be also interesting to see whether the same catalytic system could be used in the hydrogenation of unprotected $\beta$-dehydroamino acid derivatives, which would make the hydrogenation approach to $\beta$-amino acids more attractive and useful.

### 6.6 Experimental section

**General remarks** (see Chapter 2)

Metal precursor $[\text{Rh(COD)}_2]\text{BF}_4$ was purchased from Strem. $[\text{Ir(COD)}_2]\text{BArF}$ was obtained from Umicore and used as such.

Reactions were performed in a stainless steel autoclave containing 7 glass vessels (8 mL volume). These vessels were closed with septum caps. Magnetic stir bars were placed inside of each vessel and needles were placed through the septa in order to enable entrance of hydrogen. Vessels were filled under air and then flushed with nitrogen before hydrogen pressure was applied. The enantiomeric excess was determined by HPLC with chiral columns (Chiralcel OD and OD-H) and GC (Chiralcel Dex CB), in comparison with racemic products.

High throughput experiment was performed in a Premex 96 autoclave. Solutions of substrate were dispensed into the vials, followed by the solutions of the metal precursor, ligand and additive.

Ligands $\text{L}_1$,$^{50}$ $\text{L}_2$,,$^{13}$ $\text{L}_3$,$^{51}$ $\text{L}_4$,$^{50}$ and $\text{L}_5$,$^{50}$ were prepared according to the literature procedure. Ruthenium catalyst (Cat A) was prepared according to the procedure from our group.$^{52}$ Cyclic enamine 6 was obtained from DSM Pharmaceuticals and used as such.
Synthesis of N-aryl β-amino acid derivatives via asymmetric hydrogenation

Preparation of enamino-esters

Method A

\[
\text{O} \quad \text{O} \quad \text{O} \\
\text{H}_2\text{N} \quad \text{R} \\
\text{HOAc} \\
\text{ultrasonic bath, 3h}
\]

1, R = Me
2, R = Et

Alkyl acetoacetate (10 mmol), aniline (905 µL, 10 mmol) and acetic acid (57 µL, 1 mmol) were placed in a 25 mL round bottom flask. The reaction mixture was placed in an ultrasonic bath for 3h. The crude product was purified by Kugelrohr distillation.

3-Phenylamino-but-2-enoic acid methyl ester (1)\(^{30}\)

\[
\text{NH} \quad \text{O} \\
\begin{array}{c}
\text{O} \\
\text{R}
\end{array}
\]

White solid, 60% yield, Mp = 47.8 – 48.0 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) 1.99 (s, 3H), 3.68 (s, 3H), 4.70 (s, 1H), 7.08 (d, \(J = 7.39\) Hz, 2H), 7.15 (t, \(J = 7.47\) Hz, 1H), 7.32 (t, \(J = 7.87\) Hz, 2H), 10.37 (br, 1H) ppm; \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) 20.2, 50.2, 85.5, 124.4, 124.9, 129.0, 139.2, 159.0, 170.6 ppm; HRMS Calcd. for C\(_{11}\)H\(_{13}\)NO\(_2\) (M\(^+\)) 191.0946, found 191.0950.

3-Phenylamino-but-2-enoic acid ethyl ester (2)\(^{30}\)

\[
\text{NH} \quad \text{O} \\
\begin{array}{c}
\text{O} \\
\text{R}
\end{array}
\]

Yellow liquid, 76% yield; \(^1\)H NMR (400 MHz, CDCl\(_3\)) 1.28 (t, \(J = 7.12\) Hz, 3H), 1.99 (s, 3H), 4.15 (q, \(J = 7.12\) Hz, 2H), 4.70 (s, 1H), 7.08 (d, \(J = 8.05\) Hz, 2H), 7.14 (t, \(J = 7.40\) Hz, 1H), 7.31 (t, \(J = 7.55\) Hz, 2H), 10.40 (br, 1H) ppm; \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) 14.5, 20.2, 58.6, 85.9, 124.3, 124.8, 128.9, 139.2, 158.8, 170.3 ppm; HRMS Calcd. for C\(_{12}\)H\(_{15}\)NO\(_2\) (M\(^+\)) 205.1103, found 205.1110.

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Chapter 6

Preparation of enamino-esters

Method B

\[ \text{NH} \quad \text{O} \]

\[ \text{O} \quad \text{O} \quad \text{H}_2\text{N} \]

\[ \text{p-TsOH, EtOH} \quad \text{reflux overnight} \]

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

3, \( R = \text{H} \), 44% yield

4, \( R = \text{o-OMe} \), 31% yield

5, \( R = \text{p-OMe} \), 31% yield

Ethyl-benzoylacetate (5.16 mL, 30 mmol), aniline (30 mmol) and \( p \)-toluenesulfonic acid (571 mg, 3.3 mmol) were dissolved in 30 mL of ethanol and heated at 80 °C overnight. The crude product was purified by column chromatography on silica (heptane/EtOAc = 30/1), previously inactivated by triethylamine. After chromatography the product was recrystallized.

3-Phenyl-3-phenylamino-acrylic acid methyl ester (3)\(^{30}\)

\[ \text{NH} \quad \text{O} \]

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

White solid, 44% yield. After column chromatography the product was washed with heptane. Mp = 71.2 – 71.6 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) 1.34 (t, \( J = 7.11 \) Hz, 3H), 4.24 (q, \( J = 7.13 \) Hz, 2H), 5.04 (s, 1H), 6.69 (d, \( J = 7.49 \) Hz, 2H), 6.92 (t, \( J = 7.39 \) Hz, 1H), 7.09 (t, \( J = 8.40 \) Hz, 2H), 7.27 – 7.39 (m, 5H), 10.37 (br, 1H) ppm; \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) 14.4, 59.2, 91.1, 122.1, 122.8, 128.1, 128.3, 128.5, 129.3, 135.9, 140.3, 158.9, 170.0 ppm; HRMS Calcd. for \( \text{C}_{17}\text{H}_{17}\text{NO}_2 \) (M\(^+\)) 267.1259, found 267.1273.
3-(2-Methoxy-phenylamino)-3-phenyl-acrylic acid methyl ester (4)

Yellow solid, 31% yield. After column chromatography the product was recrystallized from heptane/EtOAc. Mp = 104.4 – 106.8 °C; 1H NMR (400 MHz, CDCl3) 1.32 (t, J = 7.12 Hz, 3H), 3.90 (s, 3H), 4.23 (q, J = 6.54 Hz, 2H), 5.01 (s, 1H), 6.21 (d, J = 8.00 Hz, 1H), 6.52 (t, J = 6.57 Hz, 1H), 6.82 – 6.89 (m, 2H), 7.28 – 7.38 (m, 5H), 10.28 (br, 1H) ppm; 13C NMR (100 MHz, CDCl3) 14.5, 55.6, 59.1, 91.5, 110.4, 119.7, 121.6, 122.8, 127.8, 128.2, 129.2, 129.5, 136.2, 150.3, 158.2, 169.7 ppm; HRMS Calcd. for C18H19NO3 (M+) 297.1365, found 297.1381.

3-(4-Methoxy-phenylamino)-3-phenyl-acrylic acid methyl ester (5)

Yellow solid, 31% yield. After column chromatography the product was recrystallized from heptane/EtOAc. Mp = 113.1 – 113.3 °C; 1H NMR (400 MHz, CDCl3) 1.32 (t, J = 7.13 Hz, 3H), 3.65 (s, 3H), 4.21 (q, J = 7.10 Hz, 2H), 4.97 (s, 1H), 6.61 – 6.66 (m, 4H), 7.22 – 7.33 (m, 5H), 10.28 (s, 1H) ppm; 13C NMR (100 MHz, CDCl3) 14.4, 55.0, 58.9, 89.4, 113.7, 124.1, 128.1, 128.2, 129.0, 133.3, 135.9, 155.6, 159.7, 170.1 ppm; HRMS Calcd. for C18H19NO3 (M+) 297.1365, found 297.1379.

1-Methyl-2-phenyl-piperidine (6)

This compound was obtained from DSM Pharmaceuticals.
1H NMR (400 MHz, CDCl$_3$) 1.78 – 1.85 (m, 2H), 2.17 – 2.23 (m, 2H), 2.49 (s, 3H), 3.12 – 3.15 (m, 2H), 5.03 (t, $J = 3.40$ Hz, 1H), 7.28 – 7.47 (m, 5H) ppm.

3-Phenylamino-butyric acid methyl ester (1a)$^{30}$

\[
\begin{align*}
\text{NH} & \\
\text{O} & \\
\text{O} & \\
\end{align*}
\]

1H NMR (400 MHz, CDCl$_3$) 1.28 (d, $J = 6.42$ Hz, 3H), 2.43 (dd, $J_1 = 6.94$ Hz, $J_2 = 15.05$ Hz, 1H), 2.65 (dd, $J_1 = 5.19$ Hz, $J_2 = 15.05$ Hz, 1H), 3.68 (s, 3H), 3.75 (br, 1H), 3.95 (sextet, $J = 6.03$ Hz, 1H), 6.63 (d, $J = 7.60$ Hz, 2H), 6.71 (t, $J = 7.33$, 1H), 7.17 (t, $J = 7.48$ Hz, 2H) ppm; 13C NMR (100 MHz, CDCl$_3$) 20.3, 40.5, 45.7, 51.3, 113.3, 117.4, 129.1, 146.6, 172.0 ppm; HRMS Calcd. for C$_{11}$H$_{15}$NO$_2$ (M$^+$) 193.1103, found 193.1105; HPLC (OD, eluent: heptane/i-PrOH = 99/1, detector: 210 nm, flow rate: 0.5 mL/min), $t_1 = 15.1$ min, $t_2 = 17.9$ min.

In HTE experiment conversion was determined by GC:

Column: Agilent HP-5, temperature: 120 ºC for 2min, 10ºC/min to 280 ºC (hold 2min). Retention times: starting enamine $t = 8.1$ min, product $t = 7.2$ min.

3-Phenylamino-butyric acid ethyl ester (2a)$^{30}$

\[
\begin{align*}
\text{NH} & \\
\text{O} & \\
\text{O} & \\
\end{align*}
\]

1H NMR (400 MHz, CDCl$_3$) 1.24 – 1.29 (m, 6H), 2.42 (dd, $J_1 = 6.89$ Hz, $J_2 = 14.97$ Hz, 1H), 2.63 (dd, $J_1 = 5.23$ Hz, $J_2 = 14.97$ Hz, 1H), 3.76 (br, 1H), 3.95 (sextet, $J = 6.34$ Hz, 1H), 4.14 (q, $J = 7.14$ Hz, 2H), 6.63 (d, $J = 8.60$ Hz, 2H), 6.71 (t, $J = 6.35$ Hz, 1H), 7.18 (t, $J = 7.30$ Hz, 2H) ppm; 13C NMR (100 MHz, CDCl$_3$) 14.0, 20.3, 40.8, 45.8, 60.2, 113.4, 117.4, 129.1, 146.7, 171.6 ppm; HRMS Calcd. for C$_{12}$H$_{17}$NO$_2$ (M$^+$) 207.1259, found 207.1284; HPLC (OD, eluent: heptane/i-PrOH = 98/2, detector: 210 nm, flow rate: 0.5 mL/min), $t_1 = 12.0$ min, $t_2 = 13.6$ min.

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In HTE experiment conversion was determined by GC:

Column: Agilent HP-5, temperature: 120 °C for 2min, 10°C/min to 280 °C (hold 2min). Retention times: starting enamine t = 8.8, product t = 7.9 min.

3-Phenyl-3-phenylamino-propionic acid ethyl ester (3a)

\[
\begin{align*}
&\text{NH} & \text{O} \\
&\text{O} \\
&\text{NH} & \text{O} \\
&\text{O} \\
\end{align*}
\]

\(^1\text{H}\) NMR (400 MHz, CDCl\(_3\)) 1.24 (t, \(J = 7.13\) Hz, 3H), 2.88 (d, \(J = 6.59\) Hz, 2H), 4.17 (q, \(J = 7.14\) Hz, 2H), 4.64 (br, 1H), 4.94 (t, \(J = 6.64\) Hz, 1H), 6.66 (d, \(J = 8.56\) Hz, 2H), 7.35 (t, \(J = 7.33\) Hz, 1H), 7.17 (t, \(J = 7.48\) Hz, 2H), 7.30 (t, \(J = 6.59\) Hz, 1H), 7.38 (t, \(J = 7.08\) Hz, 2H), 7.45 (d, \(J = 7.96\) Hz, 2H) ppm; \(^{13}\text{C}\) NMR (100 MHz, CDCl\(_3\)) 13.9, 42.7, 55.0, 60.4, 113.6, 117.6, 126.1, 127.2, 128.5, 128.9, 142.2, 146.8, 170.8 ppm; HRMS Calcd. for C\(_{17}\)H\(_{19}\)NO\(_2\) (M\(^+\)) 269.1416, found 269.1430; HPLC (AS-H, eluent:heptane/i-PrOH = 99/1, detector: 210 nm, flow rate: 0.5 mL/min), \(t_1 = 15.7\) min, \(t_2 = 20.2\) min.

In HTE experiment conversion was determined by GC:

Column: Agilent HP-5, temperature: 120 °C for 2min, 10°C/min to 280 ° C (hold 2min). Retention times: starting enamine t = 13.5 min, product t = 13.0 min.

3-(2-Methoxy-phenylamino)-3-phenyl-propionic acid ethyl ester (4a)

\[
\begin{align*}
&\text{O} \\
&\text{NH} & \text{O} \\
&\text{O} \\
&\text{O} \\
\end{align*}
\]

\(^1\text{H}\) NMR (400 MHz, CDCl\(_3\)) 1.27 (t, \(J = 7.15\) Hz, 3H), 2.90 - 2.94 (m, 2H), 3.45 (s, 3H), 4.17 (q, \(J = 7.60\) Hz, 2H), 4.92 (br, 1H), 5.12 (br, 1H), 6.44 (d, \(J = 8.00\) Hz, 1H), 6.67-6.85 (m, 3H), 7.24 - 7.40 (m, 5H) ppm; HRMS Calcd. for C\(_{18}\)H\(_{21}\)NO\(_3\) (M\(^+\)) 299.15214, found 299.15160.
Chapter 6

In HTE experiment conversion was determined by GC:

Column: Agilent HP-5, temperature: 180°C for 2min, 5 ºC/min to 250 ºC (hold 6min), 10 ºC/min to 300 ºC (hold 3min). Retention times: starting enamine $t = 12.3$ min, product $t = 11.0$ min.

3-(4-Methoxy-phenylamino)-3-phenyl-propionic acid ethyl ester (5a)

![Chemical structure of 3-(4-Methoxy-phenylamino)-3-phenyl-propionic acid ethyl ester (5a)](attachment:image)

$^1$H NMR (400 MHz, CDCl$_3$) 1.26 (t, $J = 7.13$ Hz, 3H), 2.89 - 2.92 (m, 2H), 3.47 (s, 3H), 4.20 (q, $J = 7.60$ Hz, 2H), 4.96 (br, 1H), 5.10 (br, 1H), 6.44 - 6.80 (m, 4H), 7.24 - 7.40 (m, 5H) ppm; HRMS Calcd. for C$_{18}$H$_{21}$NO$_3$ (M$^+$) 299.15214, found 299.15160.

In HTE experiment conversion was determined by GC:

Column: Agilent HP-5, temperature: 180°C for 2min, 5 ºC/min to 250 ºC (hold 6min), 10 ºC/min to 300 ºC (hold 3min). Retention times: starting enamine $t = 12.4$ min, product $t = 13.2$ min.

1-Methyl-2-phenyl-piperidine (6a)

![Chemical structure of 1-Methyl-2-phenyl-piperidine (6a)](attachment:image)

$^1$H NMR (400 MHz, CDCl$_3$) 1.17 – 1.36 (m, 1H), 1.46 – 1.76 (m, 5H), 1.92 (s, 3H), 2.00 – 2.08 (m, 1H), 2.68 (dd, $J_1 = 3.02$ Hz, $J_2 = 10.79$ Hz, 1H), 2.94 – 2.99 (m, 1H), 7.15 – 7.26 (m, 5H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) 25.0, 26.1, 35.8, 44.5, 57.5, 71.1, 126.9, 127.4, 128.4, 144.8 ppm; Conversion and ee determined by GC: Chirasil Dex CB, 50°C for 1min, then 10°C/min to 250°C (hold 5min). Retention times: starting enamine $t = 11.9$ min, product (enantiomers) $t_1 = 11.0$ min, $t_2 = 11.1$ min.