Asymmetric hydrogenation of imines, enamines and N-heterocycles using phosphoramidite ligands
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In this chapter asymmetric hydrogenation of imines catalyzed by iridium complexes of BINOL-derived phosphoramidites is described. Enantioselectivities up to >99% were obtained in the hydrogenation of N-aryl imines. The corresponding amines were successfully deprotected with preservation of their stereochemical integrity. N-alkyl imines were hydrogenated using the same catalytic system with up to 40% ee, while in case of cyclic imines up to 62% ee was obtained.

Part of this chapter has been published:

Chapter 4

4.1 Introduction

Chiral amines are important synthetic intermediates in the preparation of many physiologically active compounds. One of the methods for their preparation is the asymmetric hydrogenation of C=N containing functional groups (imines, oximes, hydrazones, etc.). The catalytic properties of the enantioselective homogenous hydrogenation catalysts are determined by the choice of the metal, the chiral ligand and the anion. Over the last two decades, iridium, rhodium, ruthenium, palladium and titanium have been reported to be effective in the hydrogenation of C=N functionalities.\textsuperscript{1-4}

Despite significant progress in the field, asymmetric hydrogenation of imines still represents major challenges. Although many highly efficient catalysts have been developed for the asymmetric hydrogenation of ketones and alkenes, much less examples have been reported for the metal catalyzed asymmetric hydrogenation of imines with both high enantioselectivities and acceptable turnover frequencies.\textsuperscript{1-3} As mentioned in Chapter 1 there are several reasons why imines are difficult substrates for the hydrogenation.\textsuperscript{5} One is a smaller thermodynamic gain from the reduction of C=N bond relative to the C=C bond of an olefin. There is also a less effective orbital overlap and lower affinity of the C=N for the metal center due to the η\textsuperscript{1}-binding mode of the imine bond compared to the η\textsuperscript{2}-bonding of the olefin. Since imines are poorly active towards hydrogen, often higher pressures are necessary. In addition, imines are sensitive to hydrolysis, which results in formation of an amine. Traces of amine (including the product of hydrogenation) and oligomers can behave as a catalyst poison, due to the fact that they can coordinate strongly to the metal, and in this way prevent the coordination of the ligand.\textsuperscript{6} Finally, increased steric hindrance at the unsaturated moiety may also retard the hydrogenation, which is well established with olefinic substrates. The fact that imines are often isolated as mixture of syn/anti isomers (as well as enamine isomers) can influence the outcome of the hydrogenation reaction.\textsuperscript{7}

Initially, only heterogenous catalysts like Pd/C, Pt black or Raney nickel were applied in the hydrogenation of C=N functions.\textsuperscript{8} These were modified with chiral auxiliaries anticipating that the transfer of chirality from the auxiliary to the reactant might take place. However, the
enantioselectivities obtained were low and not reproducible. The first homogenous Ru\textsuperscript{9} and Rh\textsuperscript{10} catalysts for imine hydrogenation were reported in 1975. The first significant enantioselectivities in the hydrogenation of the C=N bond were subsequently reported by Marko \textit{et al}. in 1984, using a rhodium complex with the bidentate \((2S,4S)\)-bis-(diphenylphosphino) pentane ligand (BDPP) in the hydrogenation of \(N\)-benzylacetophenone imine (up to 72\% opt. yield, Scheme 4.1).\textsuperscript{11}

\textbf{Marko \textit{et al}., 1984}

\begin{center}
\begin{tikzcd}
\text{Ph}_2\text{P} & \text{BDPP} \\
\text{Ph}_2\text{P} & \text{BDPP} \\
\end{tikzcd}
\end{center}

\textbf{Scheme 4.1} First efficient homogenous catalyst reported for the hydrogenation of C=N function

A new development emerged when Bakos and Sinou working on water-soluble catalysts, used a partially sulphonated BDPP ligand for the rhodium catalyzed hydrogenation of \(N\)-benzylacetophenoneimine in a two phase system (water, ethyl acetate).\textsuperscript{12} They found that the obtained enantioselectivity depended strongly on the degree of the sulphonation of the bisphosphine ligand (up to 96\% \textit{ee}). Following these results, de Vries \textit{et al}. isolated monosulfonated, the di-, the tri- and the tetrasulfonated ligand and tested them in the hydrogenation. Use of the monosulfonated ligand allowed hydrogenation of the imine with 95\% \textit{ee}.\textsuperscript{13} The monosulfonated ligand is a mixture of a 50\%/50\% of epimers. Surprisingly, use of the disulfonated ligand gave racemic product. The first example of an efficient hydrogenation of unprotected imines was reported by Zhang \textit{et al}. in 2009, using iridium catalyst based on (S,S)-f-Binaphane ligand (up to 95\% \textit{ee},...
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Scheme 4.2). This method allows the enantioselective synthesis of chiral amines without the use of protecting groups.

Zhang et al., 2009

\[
\begin{array}{c}
\text{NH}_2\text{Cl} \\
R_1 \quad R_2
\end{array}
\begin{array}{c}
\text{[Ir(COD)Cl]}_2, (S,S)-f-\text{Binaphane}
\end{array}
\begin{array}{c}
10 \text{ bar } \text{H}_2, \text{rt, 18h}
\end{array}
\begin{array}{c}
\text{NH}_3\text{Cl} \\
R_1 \quad R_2
\end{array}
\]

up to 95% ee

(S,S)-f-Binaphane

Scheme 4.2 The first asymmetric hydrogenation of unprotected imines

4.1.1 Asymmetric hydrogenation of N-Aryl imines

A great deal of effort was devoted to the development of a catalyst for the asymmetric hydrogenation of N-aryl imines, since N-alkyl-2,6-disubstituted anilines with a stereogenic center at the α-position are intermediates in the synthesis of acylanilide pesticides, the most important example being (S)-Metolachlor 3 (Scheme 4.3). Since not all the stereoisomers are biologically active, the stereoselective synthesis of the most active one is of great industrial importance. In 1993 a Novartis group developed a new class of iridium-ferrocenyl bisphosphines, which in the presence of both acetic acid and iodide, provided a stable effective catalyst for the asymmetric hydrogenation of the imine 1. An extensive ligand optimisation led to the choice of Ir-Xyliphos as the optimal catalyst. The production of the herbicide Metolachlor is the only commercialized asymmetric C=N bond hydrogenation.

One of the important features of Metolachlor process is the influence of iodide on enantioselectivity. It is reported that catalytic additives play a crucial role in improving the reactivity and enantioselectivity of many asymmetric reactions. As mentioned in Chapter 2, Osborn reported in
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1990 that iridium - iodo species are observed in the hydrogenation of imines.\textsuperscript{19}

\[
\begin{align*}
\text{HN-OMe} & \quad 0.01 \text{ mol\% Ir-2} \quad \text{I'/HOAc} \\
& \quad 80 \text{ bar H}_2, 50 \text{ oC} \\
\end{align*}
\]

\[
\begin{align*}
\text{HN-OMe} & \quad \text{ClCH}_2\text{COCl} \\
& \quad 80\% \text{ ee} \\
\end{align*}
\]

\[
\begin{align*}
\text{(S)}\text{-Metolachlor} \\
10\ 000 \text{ tons/year}
\end{align*}
\]

Scheme 4.3 Synthesis of (S)-Metolachlor 3

Since then, the influence of halide additives on the asymmetric hydrogenation was reported by several groups.\textsuperscript{16} We have also observed an increase in enantioselectivity with the addition of chloride salts in the asymmetric hydrogenation of quinolines (Chapter 2).\textsuperscript{20}

Another interesting feature of the Metolachlor process is the addition of acetic acid, which dramatically increases the rate of the hydrogenation. This effect may be explained with the fact that acid can protonate the product of the hydrogenation, and in this way prevent the “catalyst poisoning” with the resulting amine. It is well known that the addition of the acid often increases the enantioselectivity\textsuperscript{21} or rate\textsuperscript{22} of the asymmetric hydrogenation. It has been described as well that Brönsted acid promotes ruthenium catalyzed ionic hydrogenations of ketones and imines.\textsuperscript{23} In these cases acid protonates and therefore activates the substrate, while the following step is the hydride transfer from the metal center.

Optimal ligand in the Metolachlor process is ferrocene derived Xylihos, which has 3,5-di-methylphenyl group attached to phosphorus. Pregosin has shown in several studies that introducing 3,5-di-tert-butylphenyl or 3,5-di-methylphenyl groups onto the MeO-Biphep ligand.
(instead of the phenyl substituent) enhances the ee’s in Heck reaction, allylic alkylation, as well as palladium catalyzed hydrosilylation and ring opening chemistry (Figure 4.1).24

\[
\begin{array}{c}
Pd^+ \quad P-C \\
\end{array}
\]

\[ R = t-\text{Bu, Me} \]

**Figure 4.1** Restricted rotation around the P-C bond of the ligand

Pregosin explains this effect with the fact that there is a restricted rotation around the P-C(\textit{ipso}) bonds of the P(3,5-di-methyl-phenyl) groups. This decrease in molecular freedom derives from the restricted rotation due to the interaction of the P-aryl substituent with the ligand backbone and results in a more rigid chiral pocket and thus improved correlation between substrate and catalyst.

Metal catalyzed asymmetric hydrogenation of \( N \)-aryl imines was investigated by several research groups over the last decade. Most of the reported catalysts that give medium to high enantioselectivities are based on iridium catalysts with bidentate bisphosphine ligands, or phosphinooxazoline ligands as developed by Pfaltz.3,25-29 There are a few examples of efficient rhodium30 and palladium31 derived catalysts (91-94% ee).

Some of the most efficient ligands/catalysts reported for the asymmetric hydrogenation of \( N \)-aryl imines are depicted in Figure 4.2. In 2001 Zhang \textit{et al.} reported the use of an iridium catalyst with the ferrocenyl bidentate bisphosphine ligand \((R,R)\)-f-Binaphane in the asymmetric hydrogenation of \( N \)-aryl imines, with excellent enantioselectivity (up to >99% ee).18 Another ferrocenyl ligand was shown to be efficient in the iridium catalyzed hydrogenation of PMP-protected \( N \)-aryl imines as was applied in the synthesis of chiral lactams with excellent enantioselectivity (Knochel \textit{et al.}, up to 97% ee).25 Andersson \textit{et al.}27 and Zhou \textit{et al.}28 independently reported the use of iridium catalysts with phosphinooxazoline ligands, while Bolm \textit{et al.} described the use of iridium catalysts with diphenylphosphanylsulfoximine ligands with up to 98% ee.32 In 2002
Henschke et al. reported the use of ruthenium “Noyori-type” catalyst with \((R,R)\)-Et-DUPHOS and \((R,R)\)-diaminocyclohexane as ligands in the asymmetric hydrogenation of \(N\)-aryl imines.\(^{33}\) The first successful example of iridium catalyzed hydrogenation of \(N\)-aryl imines with catalyst bearing an achiral ligand and a chiral counterion, with excellent enantioselectivity was recently reported by Xiao et al.\(^{34}\) (up to 99% ee).

**Figure 4.2** Efficient ligands/catalysts in the asymmetric hydrogenation of \(N\)-aryl imines
In more recent studies in organocatalysis,\textsuperscript{35} the groups of Rueping, List, and MacMillan reported highly enantioselective transfer hydrogenation of imines\textsuperscript{36} or imines \textit{in situ} generated from ketones and amines\textsuperscript{37} with Hantzsch esters as reducing agents. The reduction is catalyzed by chiral phosphoric acids, which protonate the imines while the anion directs the facial attack of the hydride (Scheme 4.4).

\begin{center}
\textbf{Scheme 4.4} Rueping’s organocatalytic reduction of N-aryl imines with Hantzsch esters
\end{center}

As mentioned in Chapter 2, transfer hydrogenation is a valuable and versatile reaction which is emerging as one of the very best methods for achieving asymmetric transformations.\textsuperscript{38}

4.1.2 \textit{Asymmetric hydrogenation of N-alkyl imines}

There are not many examples in the literature of the asymmetric hydrogenation of N-alkyl imines.\textsuperscript{1,3} Most of the results are obtained on model substrates, especially N-benzyl imines (Scheme 4.5). With the exception of N-benzyl group which can be removed easily by hydrogenolysis, there is no known method for the deprotection of N-alkyl amines, leading to chiral primary amines. However, secondary amines are an interesting class of products in their own right.
Preparation of chiral amines via asymmetric hydrogenation of imines

\[
\begin{align*}
\text{R} &= \text{Cyclohexyl, Aryl} \\
\text{Ph}_2\text{P} &\quad \text{PhP} \\
\text{Ph}_2\text{P} &\quad \text{SO}_3\text{Na}^+ \\
\text{H}_2 &\quad \text{ Ru} \\
\text{N} &\quad \text{NH}_2 \\
\text{O} &\quad \text{OH} \\
\end{align*}
\]

Scheme 4.5 Efficient ligands/catalysts in the asymmetric hydrogenation of \(N\)-alkyl imines

The highest enantioselectivity was obtained with mono-sulphonated BDPP ligand (94% \(ee\)).\(^{12,13}\) Enantioselectivities exceeding 90% were reported using Buchwald’s titanocene catalyst\(^7\) and James’ rhodium catalysts with bisphosphine ligands.\(^{39}\) With a “Noyori-type” ruthenium catalyst, reported by Morris \textit{et al.}, enantioselectivity of 92% was obtained in the hydrogenation of \(N\)-benzylacetophenoneimine, with good TOF (23/h).\(^{40}\) In 2007 Reetz reported the use of an iridium catalyst based on a mixture of monodentate ligands in the hydrogenation of \(N\)-alkyl imines, with up to 92% \(ee\).\(^{41}\)

In 2003 Börner reported the \textit{in situ} reductive amination of \(\alpha\)-keto acids with \(N\)-benzylamine, catalyzed by a rhodium complex based on the
Deguphos ligand (Scheme 4.6). Often conversions were incomplete, however, ee’s up to 98% were obtained.\textsuperscript{42}

\[\text{RCOOH} + \text{BnNH}_2 \xrightarrow{\text{[Rh(P-P)\textsuperscript{*}-cat \ rt, 60 \ bar \ H}_2} \text{Ph} \xrightarrow{\text{HN\textsuperscript{-}COOH}}\]

\[\text{up to 98\% ee}\]

\[\text{R = a: PhCH}_2, \text{b: Me, c: Ph, d: HOOCCH}_2\text{CH}_2, e: \text{HOOCCH}_2, f: \text{PhCH}_2\text{CH}_2, g: \text{Me}_2\text{CHCH}_2, h: \text{Me}_3\text{CCH}_2\]

\textbf{Scheme 4.6} Direct reductive amination of \(\alpha\)-keto acids with \(N\)-benzylamine

4.1.3 Asymmetric hydrogenation of cyclic imines

Cyclic imines do not have the issue of \textit{syn/anti} isomerism, therefore higher enantioselectivities in the asymmetric hydrogenation could be expected. Some of the corresponding amines are of significant pharmaceutical importance (Figure 4.3). 1-Substituted 1,2,3,4-tetrahydroisoquinoline alkaloids, specifically \textit{Salsolidine}, have been of great interest to synthetic chemists because of their important physiological activities, especially those related to the pathogenesis of Parkinson’s disease.\textsuperscript{43} Tetrahydroisoquinoline \textit{YH 1885} is, on the other hand, a proton pump inhibitor.\textsuperscript{44}

\textbf{Figure 4.3} Tetrahydroisoquinolines of pharmaceutical importance
Preparation of chiral amines via asymmetric hydrogenation of imines

Buchwald’s titanocene catalyst gave enantioselectivities up to 99% in the hydrogenation of cyclic imines, although with low substrate/catalyst ratios and low TOF’s (Figure 4.4).45

Figure 4.4 Buchwald’s catalyst in the asymmetric hydrogenation of cyclic imines 4-6

With respect to the activity, iridium catalysts bearing bisphosphine ligands are more promising (Figure 4.5). Achiwa showed in 1998 that imides can improve enantioselectivity of the Ir-catalyzed hydrogenation of imines.46 Zhang et al. reported in 1998 the use of iridium-BICP complex in the asymmetric hydrogenation of cyclic imines in the presence of additives like phthalimide, with up to 95% ee.47 The rate of the reaction was as well influenced (full conversion in 96h without additive, 65h with 4% of phtalimide). The iridium catalysts with ferrocenyl (R,S)-Xyolphos ligand in the combination with acid or iodide as promoters gave excellent enantioselectivity in the asymmetric hydrogenation of 2,3,3-trimethyl-3H-indole 7.48 The role of additives in the hydrogenation of imines is not fully understood. There are also examples of efficient rhodium and ruthenium catalysts for the hydrogenation of cyclic imines. Xiao reported the use of the Rh-Ts-dpen catalyst in the hydrogenation of imine 8 with up to 99% ee,49 while Noyori described the use of the same ligand in the ruthenium catalyzed transfer hydrogenation of imines 8 and 9 with up to 97% ee.50 In 2006 Zhu reported the first asymmetric transfer hydrogenation of cyclic
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imines and iminium substrates in water, catalyzed by a water-soluble and recyclable ruthenium(II) complex.\textsuperscript{51}

\[ \text{(R,R)-BICP} \quad \text{Xylyphos, R = Ph, R' = Xyl} \]

up to 95\% $ee$
Noyori \textit{et al.}, 1996

up to 95\% $ee$
Zhang \textit{et al.}, 1998

up to 93\% $ee$
Blaser \textit{et al.}, 2001

Figure 4.5 Efficient ligands/catalysts in the asymmetric hydrogenation of cyclic imines 7-9

4.1.4 \textbf{Asymmetric hydrogenation of $\text{C=N-X}$ substrates}

Using Pd(OCOCF\textsubscript{3})\textsubscript{2}/(S,S)-f-Binaphane as the catalyst, Zhou and co-workers developed an efficient enantioselective synthesis of sultams \textit{via} asymmetric hydrogenation of the corresponding cyclic imines with high enantioselectivities (up to 98\% $ee$).\textsuperscript{52}

Zhang described recently an efficient Pd-catalyzed asymmetric hydrogenation of $N$-tosylimines, in the presence of bisphosphine ligand TangPhos, with full conversion and enantioselectivity of up to 99\% $ee$.\textsuperscript{53}

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However, a relatively high hydrogen pressure and catalytic loading are important limitations of that work.

Spindler and Blaser reported the development of Rh-Josiphos catalysts for the highly effective hydrogenation of several N-diphenylphosphinyl imines with ee’s up to 99%. Zhou as well reported the hydrogenation of a variety of substituted N-diphenylphosphinyl imines using Pd(OCOCF₃)₂/(S)-SegPhos as a catalyst with high enantioselectivities (up to 99% ee).

4.2 Goal of the research

Currently, only a few efficient chiral catalytic systems are available for the asymmetric hydrogenation of imines. Apart from the Metolachlor process, there are no examples of catalysts suitable for industrial applications. From earlier results in our group, it was evident that monodentate phosphoramidites give excellent results in asymmetric hydrogenation. As can be seen from previous chapters, phosphoramidites give excellent results in the hydrogenation of the C=N functional groups present in quinolines and quinoxalines. The goal of this research was to develop an efficient catalyst for the asymmetric hydrogenation of N-aryl, N-alkyl and cyclic imines. In addition, we were interested in developing an efficient deprotection method for corresponding N-aryl amines, in order to enable access to chiral primary amines of high enantiomeric purity.

4.3 Results

4.3.1 N-aryl imines

The asymmetric hydrogenation of N-phenyl-(1-phenyl-ethylidene)-amine 10 was chosen as a model reaction. Since by using the combination of [Ir(COD)Cl]₂ and PipPhos L1 we obtained excellent results in the hydrogenation of quinolines and quinoxalines at 60 °C, this catalytic system and the conditions were chosen for the initial screening in the hydrogenation of 10. The reactions were performed using 1 mol% of iridium precursor in dichloromethane over 24h (50 bar H₂, 60 °C). There are several additives reported in the literature to have an effect on the
conversion and enantioselectivity of the hydrogenation of imines. We examined the effect of some of these additives on the hydrogenation of imine 10. The results are presented in Table 4.1.

Table 4.1 Testing of the [Ir(COD)Cl]2/PipPhos catalytic system and additives in the asymmetric hydrogenation of imine 10

<table>
<thead>
<tr>
<th>Entry</th>
<th>Additive</th>
<th>Conversionb (%)</th>
<th>ee c (%)</th>
<th>Config.d</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>-</td>
<td>89</td>
<td>5</td>
<td>R</td>
</tr>
<tr>
<td>2</td>
<td>Piperidine·HCl</td>
<td>100</td>
<td>39</td>
<td>R</td>
</tr>
<tr>
<td>3</td>
<td>KI</td>
<td>58</td>
<td>37</td>
<td>R</td>
</tr>
<tr>
<td>4</td>
<td>(CH₃)₄NI</td>
<td>58</td>
<td>34</td>
<td>R</td>
</tr>
<tr>
<td>5</td>
<td>Phthalimide</td>
<td>52</td>
<td>22</td>
<td>R</td>
</tr>
<tr>
<td>6</td>
<td>HOAc</td>
<td>83</td>
<td>28</td>
<td>R</td>
</tr>
</tbody>
</table>

*Reaction conditions: 1 mmol of imine 10, 0.01 mmol of [Ir(COD)Cl]₂, 0.04 mmol of (S)-PipPhos L₁, 0.1 mmol additive, 4 mL of CH₂Cl₂ at 50 bar H₂ and 60 °C, 24h. Conversion was determined by ¹H NMR. Enantiomeric excess was determined by GC using a Chiralsil DEX CB column. Absolute configuration of the product was assigned by measuring the optical rotation and comparing it with literature data.

Without the additives the reaction proceeds with 89% conversion, however, with only 5% ee (Entry 1). In analogy with our previous findings with quinolines and quinoxalines, addition of piperidine hydrochloride improves the enantioselectivity of the reaction from 5% to 39% (Entry 2). A similar effect was obtained by addition of potassium iodide or tetramethylammonium iodide, although the reaction was significantly slower (Entries 3-4). Addition of phthalimide and organic acid increased
the enantioselectivity to 22 and 28%, respectively (Entries 5-6). In the case of phthalimide the reaction was slowed down, while upon addition of acetic acid the rate of the reaction remained unchanged.

In 2006 Faller et al. reported the use of a mixture of monodentate phosphoramidite Monophos™ and pyridine as ligands in the asymmetric hydrogenation of cyclic imines with up to 58% ee.\textsuperscript{57} We tested the combination of PipPhos L1 and two different amines in the model reaction i.e. hydrogenation of imine 10 (Scheme 4.7). Unfortunately, in both cases racemic product was obtained. In addition, when triphenylphosphine was used in combination with PipPhos L1 (Ir/L*/L = 1/2/1) only 2% conversion was obtained.

\[
\text{Amine} \quad \text{Conversion (%)} \quad \text{ee (%)}
\begin{array}{|c|c|c|}
\hline
\text{Pyridine} & 88 & 0 \\
\text{Aniline} & 100 & 0 \\
\hline
\end{array}
\]

Scheme 4.7 Testing of the combination of (S)-PipPhos L1 and amines as ligands in the asymmetric hydrogenation of 10

When different iridium precursors were tested it turned out that cationic precursors such as [Ir(COD)\textsubscript{2}]PF\textsubscript{6}, [Ir(COD)\textsubscript{2}]BF\textsubscript{4} or [Ir(COD)\textsubscript{2}]BArF gave significantly higher enantioselectivity and conversions compared to neutral [Ir(COD)Cl\textsubscript{2}] in the hydrogenation of the model compound 10 (Table 4.2).
Table 4.2 Screening of the iridium precursors in the asymmetric hydrogenation of 10\textsuperscript{a,b}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Iridium precursor</th>
<th>Conversion%</th>
<th>ee%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[Ir(COD)\textsubscript{2}]PF\textsubscript{6}</td>
<td>100</td>
<td>61</td>
</tr>
<tr>
<td>2</td>
<td>[Ir(COD)\textsubscript{2}]BF\textsubscript{4}</td>
<td>100</td>
<td>56</td>
</tr>
<tr>
<td>3</td>
<td>[Ir(COD)\textsubscript{2}]BArF</td>
<td>100</td>
<td>61</td>
</tr>
<tr>
<td>4</td>
<td>[Ir(COD)Cl\textsubscript{2}]</td>
<td>89</td>
<td>5</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Reaction conditions: 1 mmol of imine \textit{10}, 0.01 mmol of [Ir(COD)\textsubscript{2}X], 0.02 mmol of \textit{S}-PipPhos \textit{L1}, 4 mL of CH\textsubscript{2}Cl\textsubscript{2} at 50 bar and 60 °C, 24h. \textsuperscript{b} 0.01 mmol of [Ir(COD)Cl\textsubscript{2}], 0.04 mmol of PipPhos \textit{L1}. \textsuperscript{c} Conversion was determined by \textsuperscript{1}H NMR. \textsuperscript{d} Enantiomeric excess was determined by GC using a Chiralsil DEX CB column.

Since [Ir(COD)\textsubscript{2}]PF\textsubscript{6} and [Ir(COD)\textsubscript{2}]BArF gave the same enantioselectivity in the hydrogenation of \textit{10} (61% \textit{ee}), different monodentate phosphoramidites were tested in this reaction using less expensive [Ir(COD)\textsubscript{2}]PF\textsubscript{6}, under the same reaction conditions (Scheme 4.8, Table 4.3).

Full conversions were obtained in all cases except for ligands \textit{L1f} and \textit{L2d}, where only 28 and 63% conversion was obtained, respectively (Entries 6 and 9). PipPhos \textit{L1} and H\textsubscript{8}-PipPhos \textit{L2d} ligands induced the highest selectivities, however, the reaction with PipPhos \textit{L1} was significantly faster (61% and 62% \textit{ee}, Entries 1 and 9). Similar results were achieved using Monophos \textit{L1a}, and ligands \textit{L1b}, \textit{L1e} and \textit{L1g} (Entries 2, 3, 5 and 7). The use of ligand \textit{L3d}, with a 3,3'-substituted BINOL-backbone led to full conversion, however, the product was obtained with low \textit{ee} (Entry 10). Similar results were obtained with the catechol derived ligand \textit{L4h} (Entry 11).
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Scheme 4.8 Phosphoramidite ligands examined in the asymmetric hydrogenation of \( N\)-phenyl-(1-phenyl-ethylidene)-amine 10
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Table 4.3 Screening of monodentate phosphoramidite ligands in the asymmetric hydrogenation of N-phenyl-(1-phenyl-ethylidene)-amine 10

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Conversion (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>L1</td>
<td>100</td>
<td>61</td>
</tr>
<tr>
<td>2</td>
<td>L1a</td>
<td>100</td>
<td>52</td>
</tr>
<tr>
<td>3</td>
<td>L1b</td>
<td>100</td>
<td>55</td>
</tr>
<tr>
<td>4</td>
<td>L1c</td>
<td>100</td>
<td>12</td>
</tr>
<tr>
<td>5</td>
<td>L1e</td>
<td>100</td>
<td>52</td>
</tr>
<tr>
<td>6</td>
<td>L1f</td>
<td>28</td>
<td>5</td>
</tr>
<tr>
<td>7</td>
<td>L1g</td>
<td>100</td>
<td>51</td>
</tr>
<tr>
<td>8</td>
<td>L1h</td>
<td>100</td>
<td>35</td>
</tr>
<tr>
<td>9</td>
<td>L2d</td>
<td>63</td>
<td>62</td>
</tr>
<tr>
<td>10</td>
<td>L3d</td>
<td>100</td>
<td>6</td>
</tr>
<tr>
<td>11</td>
<td>L4h</td>
<td>100</td>
<td>15</td>
</tr>
</tbody>
</table>

\*Reaction conditions: 1 mmol imine 10, 0.01 mmol of [Ir(COD)2]PF6, 0.02 mmol of (S)-PipPhos L1, 4 mL of CH2Cl2 at 50 bar and 60 °C, 24h. \*Conversion was determined by 1H NMR. \*Enantiomeric excess was determined by GC using a Chiralsil DEX CB column.

Further hydrogenation experiments were performed in order to determine the optimal reaction conditions using (S)-PipPhos ligand (Table 4.4). While at 60 °C and under 50 bar of hydrogen pressure [Ir(COD)2]PF6 and [Ir(COD)2]BArF gave the same result in the hydrogenation of 10, at room temperature and lower pressures better result was obtained with [Ir(COD)2]BArF (up to 87% ee, Entry 6). The reaction with [Ir(COD)2]BArF is strongly solvent dependent: in protic solvents such as methanol no reaction was observed (Entry 12). One reason for that could be the fact that the imine partially hydrolyses which leads to the formation of an amine. Formed amine can coordinate to the iridium preventing the coordination of the PipPhos ligand. Another reason could lie in the fact that phosphoramidites are good Π-acceptors, so the methanol could coordinate too strongly to the iridium atom and cause the push-pull effect, preventing the coordination of the substrate.

Excellent conversions and high enantioselectivities (ee’s up to 87%) were obtained both in toluene and dichloromethane (Entries 7, 11). It was also observed that pressures above 5 bar caused a slight decrease in enantioselectivity in the reaction with [Ir(COD)2]BArF, however, the reaction was faster (19h at 1 bar, 2h at 25 bar, Entries 6-8). No conversion
was observed using neutral [Ir(COD)Cl]₂ as catalyst precursor at rt and 5 bar, however, as mentioned earlier, at 50 bar and 60 °C 89% conversion was obtained albeit only with 5% ee (Entries 4 and 5).

Table 4.4 Screening of the reaction conditions in the asymmetric hydrogenation of N-phenyl-(1-phenyl-ethyldene)-amine 10

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Metal precursor</th>
<th>P (bar)</th>
<th>Conv. c (%)</th>
<th>ee d (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CH₂Cl₂</td>
<td>[Ir(COD)₂]PF₆</td>
<td>1</td>
<td>100</td>
<td>64</td>
</tr>
<tr>
<td>2</td>
<td>CH₂Cl₂</td>
<td>[Ir(COD)₂]PF₆</td>
<td>5</td>
<td>100</td>
<td>65</td>
</tr>
<tr>
<td>3e</td>
<td>CH₂Cl₂</td>
<td>[Ir(COD)₂]PF₆</td>
<td>50</td>
<td>100</td>
<td>61</td>
</tr>
<tr>
<td>4</td>
<td>CH₂Cl₂</td>
<td>[Ir(COD)Cl]₂</td>
<td>5</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>5e</td>
<td>CH₂Cl₂</td>
<td>[Ir(COD)Cl]₂</td>
<td>50</td>
<td>89</td>
<td>5</td>
</tr>
<tr>
<td>6</td>
<td>CH₂Cl₂</td>
<td>[Ir(COD)₂]BArF</td>
<td>1</td>
<td>100</td>
<td>87</td>
</tr>
<tr>
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<td>CH₂Cl₂</td>
<td>[Ir(COD)₂]BArF</td>
<td>5</td>
<td>100</td>
<td>80</td>
</tr>
<tr>
<td>8</td>
<td>CH₂Cl₂</td>
<td>[Ir(COD)₂]BArF</td>
<td>25</td>
<td>100</td>
<td>73</td>
</tr>
<tr>
<td>9</td>
<td>EtOAc</td>
<td>[Ir(COD)₂]BArF</td>
<td>5</td>
<td>14</td>
<td>77</td>
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<tr>
<td>10</td>
<td>acetone</td>
<td>[Ir(COD)₂]BArF</td>
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<td>12</td>
<td>80</td>
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<tr>
<td>11</td>
<td>toluene</td>
<td>[Ir(COD)₂]BArF</td>
<td>5</td>
<td>99</td>
<td>87</td>
</tr>
<tr>
<td>12</td>
<td>MeOH</td>
<td>[Ir(COD)₂]BArF</td>
<td>5</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>13</td>
<td>THF</td>
<td>[Ir(COD)₂]BArF</td>
<td>5</td>
<td>18</td>
<td>60</td>
</tr>
</tbody>
</table>

\*Reaction conditions: 1 mmol imine 10, 0.01 mmol of [Ir(COD)₂]X, 0.02 mmol of (S)-PipPhos L₁, 4 mL of solvent, 24h. \*0.01 mmol of [Ir(COD)Cl]₂, 0.04 mmol of PipPhos L₁, 4 mL of CH₂Cl₂, 24h. \*Conversion was determined by ¹H NMR. \*Enantiomeric excess was determined by GC using a Chiralsil DEX CB column. \*Reaction performed at 60 °C.

4.3.1.1 Protective group screening

It is known that the nature of the substituent attached to nitrogen influences the properties of the C=N bond in terms of basicity, reduction potential, etc. Therefore, various N-aryl imines were hydrogenated using 1 mol% of [Ir(COD)₂]BArF and 2 mol% of PipPhos L₁, at room temperature and up to 5 bar of hydrogen pressure (Table 4.5).
Chapter 4

As mentioned in introduction, Pregosin has shown in several studies that introducing 3,5-di-tert-butylphenyl or 3,5-di-methylphenyl groups onto the MeO-Biphep ligand (instead of the phenyl substituent) enhances the ee’s in Heck reaction, allylic alkylation, as well as palladium catalyzed hydrosilylation and ring opening chemistry. In our case, the introduction of 3,5-dimethyl groups on the aryl ring of the substrate led to excellent enantioselectivities upon hydrogenation of the imine (Entries 4, 5). We assume that the reason for the excellent enantioselectivity also lies it the fact that there is a restricted rotation around the N-C bond of the N(3,5-di-methyl phenyl) group. This decrease in molecular freedom perhaps derives from the restricted rotation due to the interaction of the N-aryl substituent with the ligand backbone and results in a more rigid chiral pocket and thus improved correlation between substrate and catalyst.

Table 4.5 Asymmetric hydrogenation of different N-substituted phenyl imines

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>Ar</th>
<th>Pressure (bar)</th>
<th>Time (h)</th>
<th>ee (%)</th>
<th>Config.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10a</td>
<td>Ph</td>
<td>1</td>
<td>19</td>
<td>87</td>
<td>R</td>
</tr>
<tr>
<td>2</td>
<td>11a</td>
<td>p-MeO-Ph</td>
<td>5</td>
<td>3</td>
<td>71</td>
<td>R</td>
</tr>
<tr>
<td>3</td>
<td>12a</td>
<td>o-MeO-Ph</td>
<td>5</td>
<td>10</td>
<td>97</td>
<td>R</td>
</tr>
<tr>
<td>4</td>
<td>13a</td>
<td>3,5-(CH₃)₂-Ph</td>
<td>1</td>
<td>26</td>
<td>&gt;99</td>
<td>R</td>
</tr>
<tr>
<td>5</td>
<td>13a</td>
<td>3,5-(CH₃)₂-Ph</td>
<td>5</td>
<td>4</td>
<td>&gt;99</td>
<td>R</td>
</tr>
<tr>
<td>6</td>
<td>14a</td>
<td>3,4,5-(OMe)₃-Ph</td>
<td>1</td>
<td>6</td>
<td>99</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>14a</td>
<td>3,4,5-(OMe)₃-Ph</td>
<td>5</td>
<td>1.5</td>
<td>99</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>15a</td>
<td>3,5-(CH₃)₂,4-MeO-Ph</td>
<td>5</td>
<td>10</td>
<td>99</td>
<td>-</td>
</tr>
</tbody>
</table>

*aReaction conditions: 1 mmol imine, 0.01 mmol of [Ir(COD)₂]BAFs, 0.02 mmol of (S)-PipPhos L1, 4 mL of CH₂Cl₂ at rt. bTime to achieve full conversion. cEnantiomeric excess was determined by GC or HPLC. dAbsolute configuration of the product is assigned by measuring the optical rotation and comparing it with literature data.
As we considered it essential to have an aryl group which can be easily removed to afford the primary amines, we examined the additional introduction of a methoxy group at the 2- and 4-positions of the N-aryl group. Indeed substrates 14 and 15 could be hydrogenated with 99% ee (Entries 6-8). Although the rate of hydrogenation of trimethoxy-phenyl imine 14 was very high, the imine was shown to be susceptible to hydrolysis thus giving reproducibility problems. Since amines behave as catalyst poison we assume that the presence of aniline was the cause of the irreproducibility. As 3,5-dimethyl-4-methoxyaniline is fairly expensive we decided to test simple 2-and 4-anisidine based imines (Entries 2, 3). Although the 4-methoxy-group had a remarkable negative influence on the enantioselectivity (11a, Entry 2), hydrogenation of the imine, based on 2-anisidine gave the product 12a with 97% ee (Entry 3).

### 4.3.1.2 Scope

The scope of the reaction was examined on the series of imines based on 2-anisidine. A range of imines with electron-donating and -withdrawing substituents on the phenyl ring were studied (Table 4.6). All tested substrates (except 22) could be hydrogenated with excellent enantioselectivities (up to 99% ee, Entry 2) and turnover frequencies. Electron-donating or -withdrawing substituents in the 4-position gave comparable results (Entries 4-7).

The NMR of all imines, except 23-26, showed the presence of only one isomer. Substrates 23 and 24 were hydrogenated with excellent ee, although those imines were isolated as a mixture of isomers (Entries 10, 11). Aliphatic imines 25 and 26 were hydrogenated with full conversions, however, with much lower enantioselectivity (up to 17% ee, Entries 12, 13).
Table 4.6 Asymmetric hydrogenation of different N-o-MeO-phenyl imines

![Chemical Structure](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>R¹</th>
<th>R²</th>
<th>P (bar)</th>
<th>Time (h)</th>
<th>ee (%)</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>12a</td>
<td>Ph</td>
<td>Me</td>
<td>5</td>
<td>10</td>
<td>97</td>
</tr>
<tr>
<td>2</td>
<td>16a</td>
<td>2-Naphthyl</td>
<td>Me</td>
<td>1</td>
<td>11</td>
<td>99</td>
</tr>
<tr>
<td>3</td>
<td>16a</td>
<td>2-Naphthyl</td>
<td>Me</td>
<td>5</td>
<td>6</td>
<td>97</td>
</tr>
<tr>
<td>4</td>
<td>17a</td>
<td>4-Me-Ph</td>
<td>Me</td>
<td>5</td>
<td>10</td>
<td>98</td>
</tr>
<tr>
<td>5</td>
<td>18a</td>
<td>4-Cl-Ph</td>
<td>Me</td>
<td>5</td>
<td>3</td>
<td>97</td>
</tr>
<tr>
<td>6</td>
<td>19a</td>
<td>4-CF₃-Ph</td>
<td>Me</td>
<td>5</td>
<td>6</td>
<td>97</td>
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<td>4-F-Ph</td>
<td>Me</td>
<td>5</td>
<td>6</td>
<td>97</td>
</tr>
<tr>
<td>8</td>
<td>21a</td>
<td>3-Me-Ph</td>
<td>Me</td>
<td>5</td>
<td>30</td>
<td>93</td>
</tr>
<tr>
<td>9</td>
<td>22a</td>
<td>3-NO₂-Ph</td>
<td>Me</td>
<td>5</td>
<td>0.2</td>
<td>61</td>
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<td>10</td>
<td>23a</td>
<td>Ph</td>
<td>Et</td>
<td>5</td>
<td>19</td>
<td>94&lt;sup&gt;d&lt;/sup&gt;</td>
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<td>Pr</td>
<td>5</td>
<td>20</td>
<td>96&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
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<td>12</td>
<td>25a</td>
<td>n-butyl</td>
<td>Me</td>
<td>5</td>
<td>&lt;16</td>
<td>16&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>13</td>
<td>26a</td>
<td>n-pentyl</td>
<td>Me</td>
<td>5</td>
<td>11</td>
<td>17&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
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</table>

<sup>a</sup>Reaction conditions: 1 mmol imine, 0.01 mmol of [Ir(COD)₂]BArF, 0.02 mmol of (S)-PipPhos L₁, 4 mL of dichloromethane at rt. <sup>b</sup>Time to achieve full conversion. <sup>c</sup>Enantiomeric excess was determined by HPLC. <sup>d</sup>Imines prepared as mixture of E/Z isomers.

4.3.1.3 Deprotection of the N-o-methoxy-phenyl amines

Since chiral primary amines are important building blocks in the synthesis of various pharmaceutical intermediates and physiologically active compounds, efficient deprotection of chiral secondary amines is of major importance.

Up to date, most reports describe oxidative removal of the N-p-methoxyphenyl (PMP) and N-o-methoxyphenyl group with ceric ammonium nitrate (CAN) at low pH<sup>18,58</sup>. Disadvantages of that procedure are that usually a large excess of CAN (4-5 equiv) is required and CAN is expensive and highly toxic. Some of these disadvantages also apply to phenyl iodoacetate, which has also been reported as a deprotecting agent<sup>59,60</sup>. In recognition of these drawbacks, the Mioskowski group recently reported an
electrochemical procedure for the oxidative removal of the PMP substituent. However, electrochemical reactions are poorly amenable to scale up, requiring special production equipment.

In 2006, Rutjes reported deprotection of various N-PMP amines using different oxidation agents. Among the various PMP-protected amines, (4-methoxy-phenyl)-(1-phenyl-ethyl)-amine 11a was deprotected with 99% yield using trichloroisocyanuric acid (TCCA, Scheme 4.9). TCCA reacts with water, yielding hypochloric acid which oxidizes the amine.

Rutjes et al., 2006

\[
\begin{align*}
\text{Rutjes et al., 2006} & \\
\text{Scheme 4.9 Deprotection of the PMP-protected secondary amines by TCCA} & \\
\text{In our case, the deprotection of the } N\text{-o-methoxy-phenyl amines proceeded using trichloroisocyanuric acid as the oxidant (Table 4.7). Reactions were performed in a mixture of acetonitrile and water in the presence of sulfuric acid, giving the desired primary amine in acceptable yield (up to 71%) and preserving the stereochemical integrity. Optimal yield}
\end{align*}
\]

133
was obtained using 1 equivalent of TCCA and 1 equivalent of sulfuric acid, at 90 °C (Entry 8). This yield is comparable with the known CAN (cerium ammonium nitrate) removal of the o-methoxy substituted N-phenyl group. When the reaction was performed in the microwave, yields were somewhat lower (up to 61%).

**Table 4.7** Deprotection of o-methoxy-phenyl amines with TCCA

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>Equiv. TCCA</th>
<th>Equiv. H₂SO₄</th>
<th>Temperature (°C)</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>12a</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>20</td>
<td>54</td>
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<tr>
<td>2</td>
<td>12a</td>
<td>0.33</td>
<td>1</td>
<td>25</td>
<td>20</td>
<td>49</td>
</tr>
<tr>
<td>3</td>
<td>12a</td>
<td>1</td>
<td>1</td>
<td>25</td>
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<td>5</td>
<td>12a</td>
<td>1</td>
<td>1</td>
<td>90</td>
<td>20</td>
<td>70</td>
</tr>
<tr>
<td>6</td>
<td>12a</td>
<td>1</td>
<td>2</td>
<td>90</td>
<td>20</td>
<td>57</td>
</tr>
<tr>
<td>7</td>
<td>16a</td>
<td>1</td>
<td>1</td>
<td>90</td>
<td>20</td>
<td>68</td>
</tr>
<tr>
<td>8</td>
<td>17a</td>
<td>1</td>
<td>1</td>
<td>90</td>
<td>20</td>
<td>71</td>
</tr>
</tbody>
</table>

* 0.5 mmol amine, CH₃CN/H₂O = 1/1, 10 mL, 1M H₂SO₄.

Various oxidants were also examined in the deprotection of (2-methoxy-phenyl)-(1-phenyl-ethyl)-amine 12a in order to improve the yield of the deprotection step (Table 4.8). When ceric ammonium nitrate was employed, only 25% yield was obtained (Entry 1). With a solution of sodium hypochlorite (commercial bleach) up to 51% yield was accomplished (Entries 2-4). Periodic acid gave product with 35% yield, while the use of Fremy’s salt and various iron(III) complexes with bipyridine ligand provided only traces of product (Entries 6-9). Finally, enzyme mediated deprotection gave no product (Entry 10).
Table 4.8 Various oxidants examined in the deprotection of (2-Methoxy-phenyl)-(1-phenyl-ethyl)-amine 12a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Oxidant</th>
<th>Mol. equiv. H2SO4</th>
<th>Temp. (°C)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(NH4)2Ce(NO3)6 (3 eq.)</td>
<td>1</td>
<td>25</td>
<td>25</td>
</tr>
<tr>
<td>2</td>
<td>NaOCl (aq.) (2 eq.)</td>
<td>1</td>
<td>25</td>
<td>51</td>
</tr>
<tr>
<td>3</td>
<td>NaOCl (aq.) (2 eq.)</td>
<td>2</td>
<td>25</td>
<td>48</td>
</tr>
<tr>
<td>4</td>
<td>NaOCl (aq.) (2 eq.)</td>
<td>2</td>
<td>0</td>
<td>31</td>
</tr>
<tr>
<td>5</td>
<td>H5IO6 (1 eq.)</td>
<td>1</td>
<td>25</td>
<td>35</td>
</tr>
<tr>
<td>6</td>
<td>O-N(SO3K)2 (3 eq.)</td>
<td>1c</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>FeCl3 + 2,2'-bipyridine</td>
<td>2</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>K3[Fe(CN)6] + 2,2'-bipyridine (2 eq.)</td>
<td>1</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>Fe(NO3)3 x 9H2O + 2,2'-bipyridine (2 eq.)</td>
<td>1</td>
<td>25</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>Laccase</td>
<td>1</td>
<td>25</td>
<td>0b</td>
</tr>
</tbody>
</table>

Oxidant was added to the solution of the amine 12a and H2SO4. Reaction was performed in THF with addition of phosphate buffer (pH = 3). H2SO4 added after 16h. Oxidation potentials: E(Ce4+) = 1.38 V, E(NaOCl) = 1.12 V, E(HOCl) = 1.44 V, E(Fe(bipy)3+) = 0.66 V.

The best result in the deprotection of (2-Methoxy-phenyl)-(1-phenyl-ethyl)-amine 12a was still accomplished with the use of trichloroisocyanuric acid, although we were not succeeding in further improving the yield. One of the possible reasons for that is that the oxidized amine is in equilibrium with it’s tautomeric form, which can get hydrolysed to acetophenone and aniline (Scheme 4.10). Signals of acetophenone were observed by 1H NMR of the organic layer after reaction. It is also possible that under the reaction conditions polymerization occurs, in that way lowering the yield of the deprotection.
**Scheme 4.10** Possible side reaction in the deprotection of N-o-methoxy-phenyl amines

### 4.3.2 N-alkyl imines

We were also interested in the effect of an alkyl substituent on the nitrogen atom on enantioselectivity and conversion of the hydrogenation of imines. We were especially interested in N-benzyl imines, due to the possibility of the deprotection of the corresponding amines by hydrogenolysis. Therefore we hydrogenated benzyl-(1-phenyl-ethylidene)-amine 27, butyl-(1-phenyl-ethylidene)-amine 28 and butyl-indan-1-ylidene-amine 29 (Table 4.9). Reactions were performed using 1 mol% of \([\text{Ir(COD)}_2]\)BArF and 2 mol% of (S)-PipPhos \(\text{L1}\) in dichloromethane. Imine 27 was hydrogenated at room temperature and up to 25 bar of hydrogen pressure, however, only with up to 52% conversion and 8% ee (Entries 1, 2). In the hydrogenation of 28, conversion was achieved only at 25 bar of pressure, however, no enantioselectivity was observed even when the reaction mixture was heated (Entries 3, 5, 7). Indanone-derived imine 29 was hydrogenated with modest conversions and enantioselectivities up to 40%, at 25 bar of pressure (Entries 4, 6, 8). As mentioned earlier, Reetz reported the use of an iridium catalyst based on a mixture of monodentate ligands in the hydrogenation of N-alkyl imines, which significantly improved the enantioselectivity (up to 92% ee). In view of future improvements of our results, mixture of phosphoramidites with achiral
phosphines should be examined in the asymmetric hydrogenation of N-alkyl imines.

**Table 4.9** Asymmetric hydrogenation of N-alkyl imines

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>P (bar)</th>
<th>Temp (°C)</th>
<th>Conv. (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>27a</td>
<td>5</td>
<td>25</td>
<td>26</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>27a</td>
<td>25</td>
<td>25</td>
<td>52</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>28a</td>
<td>5</td>
<td>25</td>
<td>0</td>
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<tr>
<td>7</td>
<td>28a</td>
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</tr>
<tr>
<td>8</td>
<td>29a</td>
<td>25</td>
<td>50</td>
<td>47</td>
<td>40</td>
</tr>
</tbody>
</table>

*aReaction conditions: 1 mmol imine, 0.01 mmol of [Ir(COD)2]BArF, 0.02 mmol of (S)-PipPhos L1, 4 mL of CH2Cl2, 20h. bConversion was determined by 1H NMR. cEnantiomeric excess was determined by HPLC.

### 4.3.3 Cyclic imines

Finally, we decided to test our catalyst in the hydrogenation of cyclic imines (Table 4.10). Prochiral dihydro-isoquinolines 30-32 were hydrogenated using 1 mol% of iridium precursor and 2 mol% of (S)-PipPhos L1. Different iridium precursors and conditions were tested in the hydrogenation of 30 (Entries 1-9). The best conversions were obtained using [Ir(COD)2]BArF in dichloromethane at 40 °C, however, the highest enantioselectivity was obtained in toluene at room temperature and 5 bar.
Chapter 4

of pressure (62% ee, Entry 7). Under the same conditions dihydroisoquinoline 31 was hydrogenated with full conversion and 51% ee (Entry 10), while phenyl substituted imine 32 gave no conversion (Entry 11).

Table 4.10 Asymmetric hydrogenation of dihydroisoquinolines

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>Ir precursor</th>
<th>Solvent</th>
<th>( P ) (bar)</th>
<th>Time(^b) (h)</th>
<th>Conv.(^c) (%)</th>
<th>ee(^d) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>30a</td>
<td>[Ir(COD)(_2)]BArF</td>
<td>CH(_2)Cl(_2)</td>
<td>5</td>
<td>25</td>
<td>93</td>
<td>43</td>
</tr>
<tr>
<td>2</td>
<td>30a</td>
<td>[Ir(COD)(_2)]BArF</td>
<td>CH(_2)Cl(_2)</td>
<td>25</td>
<td>25</td>
<td>100</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>30a</td>
<td>[Ir(COD)(_2)]BArF</td>
<td>CH(_2)Cl(_2)</td>
<td>5</td>
<td>40</td>
<td>100</td>
<td>42</td>
</tr>
<tr>
<td>4</td>
<td>30a</td>
<td>[Ir(COD)(_2)]BArF</td>
<td>CH(_2)Cl(_2)</td>
<td>25</td>
<td>40</td>
<td>100</td>
<td>33</td>
</tr>
<tr>
<td>5</td>
<td>30a</td>
<td>[Ir(COD)(_2)]PF(_6)</td>
<td>CH(_2)Cl(_2)</td>
<td>5</td>
<td>25</td>
<td>88</td>
<td>50</td>
</tr>
<tr>
<td>6</td>
<td>30a</td>
<td>[Ir(COD)(_2)]PF(_6)</td>
<td>CH(_2)Cl(_2)</td>
<td>25</td>
<td>25</td>
<td>98</td>
<td>25</td>
</tr>
<tr>
<td>7</td>
<td>30a</td>
<td>[Ir(COD)(_2)]BArF</td>
<td>toluene</td>
<td>5</td>
<td>25</td>
<td>62</td>
<td>62</td>
</tr>
<tr>
<td>8</td>
<td>30a</td>
<td>[Ir(COD)(_2)]BArF</td>
<td>toluene</td>
<td>25</td>
<td>25</td>
<td>100</td>
<td>36</td>
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<tr>
<td>9</td>
<td>30a</td>
<td>[Ir(COD)(_2)]BArF</td>
<td>MeOH</td>
<td>5</td>
<td>25</td>
<td>83</td>
<td>56</td>
</tr>
<tr>
<td>10</td>
<td>31a</td>
<td>[Ir(COD)(_2)]BArF</td>
<td>toluene</td>
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<td>25</td>
<td>100</td>
<td>51</td>
</tr>
<tr>
<td>11</td>
<td>32a</td>
<td>[Ir(COD)(_2)]BArF</td>
<td>toluene</td>
<td>5</td>
<td>25</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>

\(^a\)Reaction conditions: 1 mmol imine, 0.01 mmol of [Ir(COD)\(_2\)]X, 0.02 mmol of (S)-PipPhos \( L_1 \), 4 mL of solvent at rt, 16h. \(^b\)Reaction time. \(^c\)Conversion was determined by \(^1\)H NMR. \(^d\)Enantiomeric excess was determined by HPLC.
In the hydrogenation of cyclic imine 33 using the same catalyst at room temperature and 5 bar of hydrogen pressure only 38% conversion and 10% ee was obtained (Scheme 4.11).

\[
\text{CH}_2\text{Cl}_2, \text{rt}, 5 \text{ bar } \text{H}_2, 42\text{h}
\]

1 mol% [Ir(COD)_2]BArF
2 mol% (S)-PipPhos

\[
\text{33} \rightarrow \text{33a}
\]

38% conversion, 10% ee

**Scheme 4.11 Asymmetric hydrogenation of 2,3,3-trimethyl-3H-indole 33**

### 4.4 Methylaluminoxane as counterion in asymmetric hydrogenation of imines

As mentioned earlier, phosphoramidites are cheap ligands that are easy to make in only two synthetic steps. However, [Ir(COD)_2]BArF precursor is very expensive (600 euros per 100 mg), which is making the hydrogenation of imines by using Ir/PipPhos not suitable for industrial applications. In many hydrogenations BArF counterion outperformed PF$_6$ counterion, which is attributed to its steric bulk. For these reasons the oligomeric methylaluminoxane (MAO) seemed as a good candidate for the replacement of BArF counterion.

MAO (Al(CH$_3$)$_x$O$_y$)$_n$ is a poorly-defined oligomeric material, as a number of structures are present in solution. It is best known as a co-catalyst for olefin polymerizations using metallocenes or other homogenous transition metal catalysts. MAO alkylates and then activates the metal-chloride precatalyst species, forming an ion pair. It is prepared by a (controlled) hydrolysis of trimethylaluminium (TMA) and it always contains small amounts of TMA. TMA is a methylating agent and it can be removed by reaction with phenol, in which it forms AlMe(OPh)$_2$.

We decided to examine the possibility to use MAO as a substitute for the expensive BArF counterion in imine hydrogenation (Scheme 4.12). Two imine substrates were chosen, N-aryl imine 13 and cyclic imine 30. The reaction was performed using 2.5 mol% of [Ir(COD)Cl]$_2$ at room
temperature and 5 bar of hydrogen pressure. Two different ligands were used, phosphoramidite (S)-PipPhos $L_1$ and phosphinoxazoline ligand $L_1i$. In order to remove traces of TMA from MAO, bulky phenol $34$ was used.

![Scheme 4.12 Iridium catalyzed asymmetric hydrogenation of $13$ and $30$ using MAO as a counterion](image)

Two different concentrations of the MAO solution were employed and three different amounts were screened (5, 50 and 500 equivalents with respect to $[\text{Ir}(\text{COD})\text{Cl}]_2$). Catalysts were prepared in the glovebox and the hydrogenation was performed in the Premex 96-Multi Reactor with 96 reaction vessels. Solutions of MAO were dispersed by automatic dispenser into the vials, following by the addition of a phenol $34$ solution. The substrate solution was then added, followed by addition of the catalyst (pre-mixed solution of $[\text{Ir}(\text{COD})\text{Cl}]_2$ and ligand). Hydrogenation was carried out over 16h. Results obtained with 5, 50 and 500 equivalents of MAO are presented in Tables 4.11, 4.12 and 4.13.
**Table 4.11** Asymmetric hydrogenation of imines using 5 equivalents of MAO\(^{a,b}\)

<table>
<thead>
<tr>
<th>Phenol</th>
<th>Solvent</th>
<th>Substrate</th>
<th>Conversion(^c) (%)</th>
<th>(\text{Ir/L1})</th>
<th>(\text{Ir/L1i})</th>
<th>(\text{Ir/L1})</th>
<th>(\text{Ir/L1i})</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>MAO A</td>
<td>MAO B</td>
<td>MAO A</td>
<td>MAO B</td>
</tr>
<tr>
<td>With</td>
<td>CH(_2)Cl(_2)</td>
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<td>0</td>
<td>2</td>
<td>17</td>
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<tr>
<td></td>
<td>CH(_2)Cl(_2)</td>
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<td>61</td>
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<tr>
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<td>Toluene</td>
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<td>8</td>
<td>22</td>
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<tr>
<td>Without</td>
<td>CH(_2)Cl(_2)</td>
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<td>2</td>
<td>3</td>
<td>4</td>
<td></td>
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<tr>
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<td>26</td>
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<td></td>
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<table>
<thead>
<tr>
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<th>Solvent</th>
<th>Substrate</th>
<th>Ee(^d)(%)</th>
<th>(\text{Ir/L1})</th>
<th>(\text{Ir/L1i})</th>
<th>(\text{Ir/L1})</th>
<th>(\text{Ir/L1i})</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
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<td>MAO A</td>
<td>MAO B</td>
<td>MAO A</td>
<td>MAO B</td>
</tr>
<tr>
<td>With</td>
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<td>54</td>
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<td>CH(_2)Cl(_2)</td>
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<td>15</td>
<td>-</td>
<td>-7</td>
<td>79</td>
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\(^{a}\)Reaction conditions: 100 \(\mu\)mol imine, 2.5 \(\mu\)mol \(\text{Ir(COD)Cl}_2\), 10 \(\mu\)mol \((S)-\text{PipPhos L1}\), 12.5 \(\mu\)mol MAO, 25 \(\mu\)mol phenol 34, 2.45 mL of solvent, rt, 5 bar H\(_2\), 16h.  \(^{b}\)100 \(\mu\)mol imine, 2.5 \(\mu\)mol \(\text{Ir(COD)Cl}_2\), 5 \(\mu\)mol \(\text{L1i}\), 12.5 \(\mu\)mol MAO, 25 \(\mu\)mol phenol 34, 2.45 mL of solvent, rt, 5 bar H\(_2\), 16h.  \(^{c}\)Conversion was determined by GC and HPLC.  \(^{d}\)Enantiomeric excess was determined by HPLC.  \(\text{MAO A} = 1.5 \text{ M in toluene, MAO B} = 2.3 \text{ M in heptane.}

Using 5 equivalents of MAO, with respect to the metal precursor, modest conversions were achieved. In the hydrogenation of cyclic substrate 30 the highest enantioselectivity was obtained using phosphino-oxazoline ligand \(\text{L1i}\) in toluene, without use of phenol (79% \(ee\)), however, conversion was very low (4%). In the hydrogenation of \(N\)-aryl imine 13 the highest enantioselectivity was obtained using PipPhos \(\text{L1}\) in dichloromethane, in the presence of phenol (17% conversion, 54% \(ee\)).
Table 4.12 Asymmetric hydrogenation of imines using iridium catalyst and 50 equivalents of MAO\textsuperscript{a,b}

<table>
<thead>
<tr>
<th>Conversion\textsuperscript{c} (%)</th>
<th>5 equivalents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenol</td>
<td>Solvent</td>
</tr>
<tr>
<td>MAO A</td>
<td>MAO B</td>
</tr>
<tr>
<td>With</td>
<td></td>
</tr>
<tr>
<td>CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>13</td>
</tr>
<tr>
<td>CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>30</td>
</tr>
<tr>
<td>Toluene</td>
<td>13</td>
</tr>
<tr>
<td>Toluene</td>
<td>30</td>
</tr>
<tr>
<td>Without</td>
<td></td>
</tr>
<tr>
<td>CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>13</td>
</tr>
<tr>
<td>CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>30</td>
</tr>
<tr>
<td>Toluene</td>
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</tr>
<tr>
<td>Toluene</td>
<td>30</td>
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<table>
<thead>
<tr>
<th>Ee\textsuperscript{d} (%)</th>
<th>5 equivalents</th>
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<tbody>
<tr>
<td>Phenol</td>
<td>Solvent</td>
</tr>
<tr>
<td>MAO A</td>
<td>MAO B</td>
</tr>
<tr>
<td>With</td>
<td></td>
</tr>
<tr>
<td>CH\textsubscript{2}Cl\textsubscript{2}</td>
<td>13</td>
</tr>
<tr>
<td>CH\textsubscript{2}Cl\textsubscript{2}</td>
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</tr>
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<td>Toluene</td>
<td>13</td>
</tr>
<tr>
<td>Toluene</td>
<td>30</td>
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<tr>
<td>Without</td>
<td></td>
</tr>
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</tr>
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<tr>
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<td>30</td>
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\textsuperscript{a}Reaction conditions: 100 \( \mu \)mol imine, 2.5 \( \mu \)mol \([\text{Ir}([\text{COD})\text{Cl}])_2\), 10 \( \mu \)mol \((S)-\text{PipPhos L1}\), 125 \( \mu \)mol MAO, 250 \( \mu \)mol phenol 34, 2.45 mL of solvent, rt, 5 bar H\textsubscript{2}, 16h. \textsuperscript{b}100 \( \mu \)mol imine, 2.5 \( \mu \)mol \([\text{Ir}([\text{COD})\text{Cl}])_2\), 5 \( \mu \)mol \(L1i\), 125 \( \mu \)mol MAO, 250 \( \mu \)mol phenol 34, 2.45 mL of solvent, rt, 5 bar H\textsubscript{2}, 16h. \textsuperscript{c}Conversion was determined by GC and HPLC. \textsuperscript{d}Enantiomeric excess was determined by HPLC. \textsuperscript{e}MAO A = 1.5 M in toluene, MAO B = 2.3 M in heptane.

When 50 equivalents of MAO were used, high conversions were achieved with both substrates. High enantioselectivity was obtained in the hydrogenation of \(N\)-aryl imine 13 using phosphinooxazoline \(L1i\) in dichloromethane, without the use of phenol (98% conversion, 76% \(ee\)). Dihydroisoquinoline 30 was hydrogenated with up to 32% \(ee\) (87% conversion) in toluene, using PipPhos \textbf{L1}.
Preparation of chiral amines via asymmetric hydrogenation of imines

### Table 4.13 Asymmetric hydrogenation of imines using iridium catalyst and 500 equivalents of MAO\(^a, b\)

<table>
<thead>
<tr>
<th>Phenol</th>
<th>Solvent</th>
<th>Substrate</th>
<th>(\text{Ir/L1})</th>
<th>(\text{Ir/L1i})</th>
<th>(\text{Ir/L1})</th>
<th>(\text{Ir/L1i})</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>MAO A</td>
<td>MAO B</td>
<td>MAO A</td>
<td>MAO B</td>
</tr>
<tr>
<td>With</td>
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<td>81</td>
<td>94</td>
<td>95</td>
</tr>
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<td></td>
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<td>40</td>
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<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
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<td>Toluene</td>
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<td>5</td>
<td>3</td>
<td>17</td>
<td>48</td>
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<td></td>
<td></td>
<td></td>
<td>Ee(^d) (%)</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
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<td>MAO A</td>
<td>MAO B</td>
<td>MAO A</td>
<td>MAO B</td>
</tr>
<tr>
<td>With</td>
<td>CH(_2)Cl(_2)</td>
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<td>15</td>
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<td>Toluene</td>
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<td>-</td>
<td>-</td>
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<td>66</td>
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<tr>
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</tbody>
</table>

\(^a\)Reaction conditions: 100 \(\mu\)mol imine, 2.5 \(\mu\)mol [Ir(COD)Cl]\(_2\), 10 \(\mu\)mol ([S-PipPhos L1], 1250 \(\mu\)mol MAO, 2500 \(\mu\)mol phenol \(34\), 2.45 mL of solvent, rt, 5 bar H\(_2\), 16h. \(^b\)100 \(\mu\)mol imine, 2.5 \(\mu\)mol [Ir(COD)Cl]\(_2\), 5 \(\mu\)mol [S-PipPhos L1i], 1250 \(\mu\)mol MAO, 2500 \(\mu\)mol phenol \(34\), 2.45 mL of solvent, rt, 5 bar H\(_2\), 16h. \(^c\)Conversion was determined by GC and HPLC. \(^d\)Enantiomeric excess was determined by HPLC. \(^e\)MAO A = 1.5 M in toluene, MAO B = 2.3 M in heptane.

When 500 equivalents of MAO were used, conversions to desired product were mostly very low, especially of the cyclic imine 30. In the cases where there was no product observed, the starting material was also decomposed. The highest enantioselectivity was obtained in the hydrogenation of \(N\)-aryl imine 13 using phosphinoxazoline ligand L1i in dichloromethane, without presence of phenol (89% ee, 40% conversion). Dihydroisoquinoline 30 was hydrogenated with up to 84% ee (70% conversion) in dichloromethane with phosphinoxazoline ligand L1i, with addition of phenol. It seems that in most of the cases slightly better results are obtained when phenol was used as additive, however this effect needs to be further investigated.
These results show that MAO is a good potential substitute for an expensive BArF counterion in the asymmetric hydrogenation of imines. For the good evaluation of the reactions with MAO, it is essential to perform additional experiments. Oxazoline ligand L1 should be examined in the hydrogenation of imines with BArF as counterion so that the result could be compared with the results obtained with MAO as a counterion. Different phenols could also be tested, as well as solvents, temperatures and equivalents of MAO. The disadvantage of this method is the fact that a large excess of MAO is needed. Enantioselectivities are modest in most of the cases. In addition, phenol is added to the reaction mixture, making the product less easy to purify.

4.5 Conclusion

In conclusion, we have developed a new hydrogenation method for a range of acyclic \(N\)-aryl imines with excellent enantioselectivities and high TOF’s, using an \textit{in situ} prepared iridium catalyst based on the monodentate phosphoramidite ligand PipPhos. The advantage of the method described in this chapter compared to the previously reported results in the imine hydrogenation field is that PipPhos ligand is cheap and easily accessible. It can be synthesized in two steps starting from cheap BINOL, in high yield. In addition, the hydrogenations are performed at low pressure and room temperature. We have proven that aryl imines isolated as mixtures of isomers can also be hydrogenated with excellent enantioselectivity. Full conversions were obtained and ee’s up to \(>99\%\) were reached. Products were deprotected smoothly with preservation of stereochemical integrity. On the contrary, aliphatic \(N\)-o-methoxy-phenyl imines were hydrogenated with low enantioselectivity using the iridium/PipPhos catalytic system.

The same catalytic system was not successful in the hydrogenation of \(N\)-alkyl imines, where low conversions and enantioselectivities only up to 40\% were obtained. Cyclic imines were hydrogenated with full conversions and ee’s up to 62\%.

Methylaluminoxane was shown to be an efficient potential substitute for the expensive BArF counterion in the imine hydrogenation. Further
experiments have to be carried out in order to compare performance of the catalyst with BArF and MAO as counterions, in more detail.

4.6 Experimental section

General remarks (see Chapter 2)

The metal precursor \([\text{Ir}(\text{COD})_2\text{BArF}]_2\) was obtained from Umicore.

The catalyst was prepared \textit{in situ}. Reactions were performed in stainless steal autoclave containing 7 glass vessels (8 mL volume). The vessels were closed with caps containing septa. Magnetic stirrers were placed inside 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 AD, OD-H, AS-H, OJ-H) or by GC with Chiralsil DEX CB, in comparison with racemic products. Racemic amines were prepared by reduction of the imines with sodium borohydride in ethanol.

Ligands \(\text{L}_1, \text{L}_{1a}-\text{L}_{1e}, \text{L}_1f, \text{L}_1g, \text{L}_1h, \text{L}_2d, \text{L}_3d, \text{L}_4h\) were prepared according to the literature procedure. Imines \(30-33\) were purchased and used in hydrogenation without purification.

General experimental procedure for the preparation of the imines

A 100 mL round-bottom flask was filled with ketone (50 mmol) and amine (60 mmol) and molecular sieves (4Å, 20 g) in toluene (30 mL). The reaction mixture was stirred at room temperature overnight, filtered and the solvent was evaporated. The crude product was purified by Kugelrohr distillation. Solid imines were recrystallized from dry pentane or ether.

General experimental procedure for hydrogenation

A mixture of iridium precursor (0.01 mmol), chiral ligand \((\text{Ir}/\text{L}^* = 1/2)\), and substrate (1 mmol) was dissolved in solvent, in a glass vial and provided with a stirring bar. The vial was placed in a stainless steel autoclave. After the reaction, hydrogen pressure was carefully released. Solvent was removed in vacuo and conversion was determined by \(^1\text{H}\) NMR. Product was purified by chromatography column over silica gel
(heptane/EtOAc). Absolute configurations were determined by measuring optical rotation and comparison with literature data.

**General procedure for the deprotection of the hydrogenation products 12a and 16a**

In 10 mL of a mixture of acetonitrile and water (1/1), 0.50 mmol of secondary amine was dissolved. Then 500 µL of 1M sulphuric acid and 118 mg (0.50 mmol) of trichloroisocyanuric acid were added to the solution. The reaction was heated at 90 °C for 18h. The cooled reaction mixture was extracted with dichloromethane (3 x 100 mL). The resulting aqueous phase was subsequently brought to pH 10.5 through the addition of 2M aqueous KOH and extracted with ethyl acetate (3 x 100 mL). The organic layer was acidified with conc. HCl, dried and concentrated. The product was isolated as its hydrochloride salt.

**General procedure for the hydrogenation experiments with the use of MAO as a counterion**

Reactions were performed using 2.5 mol% of [Ir(COD)Cl]₂ (2.5 µmol, 1.67 mg) at room temperature and 5 bar of hydrogen pressure. PipPhos L₁ (10 µmol, 3.99 mg) and [Ir(COD)Cl]₂ (2.5 µmol, 1.67 mg) were dissolved in 200 µmol of solvent was pipetted per each vial. Phosphinoxazoline ligand L₁₁ (5 µmol, 1.86 mg) and [Ir(COD)Cl]₂ (2.5 µmol, 1.67 mg) were dissolved in 200 µmol of solvent was pipetted per each vial.

**For 5 eq. of MAO:**

- Phenol 34 (25 µmol, 5.51 mg, per reaction vial), added as a solution in DCM or toluene (100 µL, 0.055 M).
- **MAO A** (1.5 M in toluene), for 5 eq. of MAO:
  - 300 µL of MAO B diluted with 3.60 mL of heptane. 100 µL of solution was pipetted per each reaction vial.
- **MAO B** (2.3 M in heptane), for 5 eq. of MAO:
  - 200 µL of MAO B diluted with 3.68 mL of heptane. 100 µL of solution was pipetted per each reaction vial.
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**For 50 eq of MAO:**

Phenol 34 (250 µmol, 55.1 mg per reaction vial), added as a solution in DCM or toluene (100 µL, 0.055 M).

**MAO A** (1.5 M in toluene), for 50 eq. of MAO:
83 µL of solution was pipetted per each reaction vial.

**MAO B** (2.3 M in heptane), for 50 eq. of MAO:
54 µL of solution was pipetted per each reaction vial.

**For 500 eq of MAO:**

Phenol 34 (2.5 mmol, 551 mg per reaction vial), added as a solid.

**MAO A** (1.5 M in toluene), for 500 eq. of MAO:
833 µL of solution was pipetted per each reaction vial.

**MAO B** (2.3 M in heptane), for 500 eq. of MAO:
544 µL of solution was pipetted per each reaction vial.

**Substrates** were added as a solution in DCM or toluene (100 µmol of substrate, 2.25 mL of solvent).

Solutions were pipetted in the glovebox and the hydrogenation was performed in the Premex 96-Multi Reactor with 96 reaction vessels. Solutions of MAO were dispersed by automatic dispenser into the vials, following by the addition of phenol 34 solution. Substrate solution was then added, followed by addition of catalyst (pre-mixed solution of 
[Ir(COD)Cl]_2 and ligand). Hydrogenation was carried out over 16h.

**N-Phenyl-(1-phenyl-ethyldene)-amine (10)**

\[
\begin{align*}
  &\text{Light yellow solid, 80% yield, Mp = 40.1 - 40.5 °C; }^1\text{H NMR (400 MHz, CDCl}_3) 2.27 (s, 3H), 6.84 - 6.86 (m, 2H), 7.11 - 7.15 (m, 1H), 7.37 - 7.41 (m, 2H), 7.48 - 7.51 (m, 3H), 8.01 - 8.04 (m, 2H) ppm; }^{13}\text{C NMR (100 MHz, CDCl}_3) 18.3, 120.3, 124.2, 128.1, 129.3, 129.9, 131.4, 140.4, 152.7, 166.4 ppm; \text{HRMS Calcd. for C}_{14}\text{H}_{13}\text{N (M+1) 195.1048, found 195.1056.} 
\end{align*}
\]
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\[N-(4-\text{Methoxy-phenyl})-(1-\text{phenyl-ethylidene})\text{-amine (11)}^{25,72}\]

\[
\begin{align*}
\text{Yellow solid, 46% yield, } & \text{Mp = 86.5 – 86.7 °C; } \\
\text{ } & \text{1H NMR (400 MHz, CDCl}_3\text{)} \\
\text{ } & 2.26 \text{ (s, 3H), 3.82 \text{ (s, 3H), 6.75 – 6.78 (m, 2H), 6.90 – 6.93 (m, 2H), 7.44 – 7.46 (m, 3H), 7.95 – 7.99 (m, 2H) ppm; } \\
\text{ } & \text{13C NMR (100 MHz, CDCl}_3\text{)} 18.2, 56.4, 115.2, 121.7, 128.0, 129.3, 131.2, 140.7, 145.8, 156.9, 166.6 \text{ ppm; } \\
\text{HRMS Calcd. for C}_{15}\text{H}_{15}\text{NO (M+1)} & \text{225.1154, found 225.1143.}
\end{align*}
\]

\[N-(2-\text{Methoxy-phenyl})-(1-\text{phenyl-ethylidene})\text{-amine (12)}^{72}\]

\[
\begin{align*}
\text{Yellow solid, 60% yield, } & \text{Mp = 48 – 48.5 °C; } \\
\text{ } & \text{1H NMR (400 MHz, CDCl}_3\text{)} 2.20 \text{ (s, 3H), 3.80 \text{ (s, 3H), 6.78 – 6.82 (m, 1H), 6.93 – 7.10 (m, 3H), 7.44 – 7.50 (m, 3H), 8.01 – 8.06 (m, 2H) ppm; } \\
\text{ } & \text{13C NMR (100 MHz, CDCl}_3\text{)} 18.7, 56.6, 112.5, 121.5, 121.8, 125.1, 128.2, 129.2, 131.3, 140.4, 141.6, 149.9, 168.0 \text{ ppm; } \\
\text{HRMS Calcd. for C}_{15}\text{H}_{15}\text{NO (M+1)} & \text{225.1154, found 225.1145.}
\end{align*}
\]

\[N-(3,5-\text{Dimethyl-phenyl})-(1-\text{phenyl-ethylidene})\text{-amine (13)}^{25}\]

\[
\begin{align*}
\text{Yellow oil, 75% yield; } & \text{1H NMR (400 MHz, CDCl}_3\text{)} 2.25 \text{ (s, 3H), 2.34 \text{ (s, 6H), } } \\
\text{ } & \text{6.44 \text{ (s, 2H), 6.75 \text{ (s, 1H), 7.44 – 7.48 (m, 3H), 7.96 – 8.0 (m, 2H) ppm; } } \\
\text{ } & \text{13C NMR (100 MHz, CDCl}_3\text{)} 18.3, 22.3, 117.9, 125.8, 128.1, 129.3, 131.3, 139.5, 140.6, 152.7, 165.9 \text{ ppm; } \\
\text{HRMS Calcd. for C}_{16}\text{H}_{17}\text{N (M+1)} & \text{223.1361, found 223.1359.}
\end{align*}
\]
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$N$-(1-Phenyl-ethyldene)-(3,4,5-trimethoxy-phenyl)-amine (14)

![Chemical Structure Image]

Light yellow solid, 34% yield, Mp = 101.6 – 103 °C; $^1$H NMR (400 MHz, CDCl$_3$) 2.26 (s, 3H), 3.81 (m, 9H), 6.02 (s, 2H), 7.42 – 7.43 (m, 3H), 7.94 – 7.96 (m, 2H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) 18.3, 56.9, 61.8, 97.4, 128.0, 129.2, 131.4, 134.6, 140.1, 148.8, 154.4, 166.8 ppm, HRMS Calcd. for C$_{17}$H$_{19}$NO$_3$ (M+1) 285.1365, found 285.1371.

$N$-(4-Methoxy-3,5-dimethyl-phenyl)-(1-phenyl-ethyldene)-amine (15)

![Chemical Structure Image]

Light yellow solid, 79% yield, Mp = 65.7 – 66.2 °C; $^1$H NMR (400 MHz, CDCl$_3$) 2.26 (s, 3H), 2.29 (s, 6H), 3.73 (s, 3H), 6.45(s, 2H), 7.43 – 7.46 (m, 3H), 7.93 – 7.98 (m, 2H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) 16.4, 17.6, 60.1, 119.7, 127.3, 128.5, 130.5, 131.4, 139.9, 147.5, 153.2, 165.4 ppm; HRMS Calcd. for C$_{17}$H$_{19}$NO (M+1) 253.1467, found 253.1457.

$N$-(2-Methoxy-phenyl)-(1-naphthalen-2-yl-ethyldene)-amine (16)

![Chemical Structure Image]

Light yellow solid, 76% yield, Mp = 103.8 – 103.9 °C; $^1$H NMR (400 MHz, CDCl$_3$) 2.32 (s, 3H), 3.82 (s, 3H), 6.82 – 6.87 (m, 1H), 6.95 – 7.12 (m, 3H), 7.51 – 7.56 (m, 2H), 7.86 – 7.97 (m, 3H), 8.26 – 8.32 (m, 1H), 8.39 (s, 1H)
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ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) 18.7, 56.6, 112.5, 121.6, 121.9, 125.2, 125.4, 127.2, 128.0, 128.6, 128.9, 129.9, 133.9, 135.4, 137.7, 141.6, 149.9, 167.8 ppm; HRMS Calcd. for C$_{19}$H$_{17}$NO (M+1) 275.1310, found 275.1309.

$N$-(2-Methoxy-phenyl)-(1-p-tolyl-ethylidene)-amine (17)

Yellow oil, 60% yield; $^1$H NMR (400 MHz, CDCl$_3$) 2.17 (s, 3H), 2.42 (s, 3H), 3.79 (s, 3H), 6.78 – 6.80 (m, 1H), 6.93 – 7.10 (m, 3H), 7.25 – 7.27 (m, 2H), 7.92 – 7.94 (m, 2H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) 18.6, 22.3, 56.6, 112.6, 121.6, 121.8, 124.9, 128.2, 129.9, 137.7, 141.5, 141.7, 150.0, 167.7 ppm; HRMS Calcd. for C$_{19}$H$_{17}$NO (M+1) 239.1310, found 239.1309.

$N$-[1-(4-Chloro-phenyl)-ethylidene]-[2-methoxy-phenyl]-amine (18)

Light yellow solid, 46% yield, Mp = 62.8 – 62.9 °C; $^1$H NMR (400 MHz, CDCl$_3$) 2.16 (s, 3H), 3.79 (s, 3H), 6.76 – 6.78, (m, 1H), 6.93 – 6.99 (m, 2H), 7.07 – 7.11 (m, 1H) 7.40 – 7.42 (m, 2H), 7.95 – 7.97 (m, 2H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) 18.6, 56.5, 112.5, 121.4, 121.8, 125.3, 129.4, 129.6, 137.4, 138.7, 141.2, 149.8, 166.8 ppm; HRMS Calcd. for C$_{15}$H$_{14}$ClNO (M+1) 259.0764, found 259.0772.
Preparation of chiral amines via asymmetric hydrogenation of imines

\[ N-(2\text{-}\text{Methoxy-phenyl})-\text{[1-(4-Trifluoromethyl-phenyl)-ethylidene]-amine} \] (19)

Light yellow solid, 34% yield, Mp = 87.1 – 87.3 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) 2.20 (s, 3H), 3.80 (s, 3H), 6.76 – 6.80 (m, 1H), 6.94 – 7.15 (m, 3H), 7.68 – 7.72 (m, 2H), 8.10 – 8.14 (m, 2H) ppm; \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) 18.8, 56.5, 112.5, 121.3, 121.9, 125.0 (q, \(J = 272.2\) Hz), 125.5 (q, \(J = 3.7\) Hz), 125.5, 128.6, 132.9 (q, \(J = 32.6\) Hz), 141.0, 143.5, 149.6, 166.9 ppm; \(^{19}\)F (376 MHz, CDCl\(_3\)) -63.1 ppm; HRMS Calcd. for C\(_{16}\)H\(_{14}\)F\(_3\)NO (M+1) 293.1028, found 293.1014.

\[ N-\text{[1-(4-Fluoro-phenyl)-ethylidene]-[2-methoxy-phenyl]-amine} \] (20)

Light yellow solid, 55% yield, Mp = 65.7 – 65.9 °C; \(^1\)H NMR (400 MHz, CDCl\(_3\)) 2.17 (s, 3H), 3.80 (s, 3H), 6.77 – 6.80 (m, 1H), 6.94 – 7.0 (m, 2H), 7.07 – 7.14 (m, 3H), 8.01 – 8.05 (m, 2H) ppm; \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) 17.9, 55.8, 111.8, 115.4 (d, \(J = 21.5\) Hz), 120.8, 121.2, 124.5, 129.6, 129.7, 135.8, 140.6, 149.2, 164.5 (d, \(J = 250.36\) Hz), 166.0 ppm; \(^{19}\)F (376 MHz, CDCl\(_3\)) -111.0 ppm; HRMS Calcd. for C\(_{15}\)H\(_{14}\)FNO (M+1) 243.1059, found 243.1048.
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\textit{N-}(2-Methoxy-phenyl)-(1-\textit{m}-tolyl-ethylidene)-amine (21)

\begin{center}
\text{\textbf{N}} - (2-Methoxy-phenyl)-[1-(3-nitro-phenyl)-ethylidene]-amine (22)
\end{center}

\begin{center}
\textit{N-}(2-Methoxy-phenyl)-(1-phenyl-propylidene)-amine (23)
\end{center}

Light yellow solid, 61% yield, Mp = 64.8 – 64.9 °C; $^1$H NMR (400 MHz, CDCl$_3$) 2.17 (s, 3H), 2.42 (s, 3H), 3.79 (s, 3H), 6.76 – 6.79 (m, 1H), 6.92 – 6.98 (m, 2H), 7.05 – 7.09 (m, 1H), 7.26 – 7.35 (m, 2H), 7.75 – 7.77 (m, 1H), 7.88 (s, 1H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) 18.8, 22.4, 56.5, 112.4, 121.5, 121.8, 125.0, 125.4, 128.7, 129.1, 132.1, 138.9, 140.3, 141.6, 149.8, 168.2 ppm; HRMS Calcd. for C$_{16}$H$_{17}$NO (M+1) 239.1310, found 239.1297.

Yellow solid, 76% yield, Mp = 89.7 – 90.1 °C; $^1$H NMR (400 MHz, CDCl$_3$) 2.23 (s, 3H), 3.80 (s, 3H), 6.77 – 6.80 (m, 1H), 6.95 – 7.00 (m, 2H), 7.09 – 7.12 (m, 1H), 7.59 – 7.64 (m, 1H), 8.28 – 8.31 (m, 1H), 8.36 – 8.39 (m, 1H), 8.81 – 8.83 (m, 1H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) 18.7, 56.5, 112.4, 121.3, 121.8, 123.2, 125.7, 125.8, 130.2, 134.1, 140.5, 141.9, 149.3, 149.5, 165.8 ppm; HRMS Calcd. for C$_{15}$H$_{14}$N$_2$O$_3$ (M+1) 271.10772, found 271.10760.

Light yellow solid, 47% yield, Mp = 55.7 – 57.0 °C, mixture of isomers (6.7/1); $^1$H NMR (400 MHz, CDCl$_3$) 1.05 (t, $J$ = 7.68 Hz, 3H (major isomer)).
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1.25 (t, $J = 7.42$ Hz, 3H (minor isomer)), 2.60 (q, $J = 7.67$ Hz, 2H (major isomer)), 2.84 (q, $J = 7.42$ Hz, 2H (minor isomer)), 3.70 (s, 3H (minor isomer)), 3.79 (s, 3H (major isomer)), 6.75 – 6.77 (m, 1H), 6.93 – 6.98 (m, 2H), 7.05 – 7.09 (m, 1H), 7.44 – 7.46 (m, 3H), 7.95 – 7.98 (m, 2H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) 13.1, 25.1, 56.5, 112.4, 121.1, 121.8, 124.8, 128.7, 129.3, 131.2, 139.0, 141.6, 149.7, 173.1 ppm; HRMS Calcd. for C$_{16}$H$_{17}$NO (M+1) 239.1310, found 239.1314.

$N$-(2-Methoxy-phenyl)-(1-phenyl-butylidene) amine (24)

Yellow oil, 27% yield, 7% of enamine present, mixture of isomers 3.9:1; $^1$H NMR (400 MHz, CDCl$_3$) 0.81 (t, $J = 7.41$ Hz, 3H (major isomer)), 1.06 (t, $J = 7.39$ Hz, 3H (minor isomer)), 1.44 – 1.54 (m, 2H (major isomer)), 1.66 – 1.72 (m, 2H (minor isomer)), 2.22 (t, $J = 7.35$ Hz, 2H (minor isomer)), 2.54 – 2.58 (m, 2H (major isomer)), 3.78 (s, 3H, (major isomer)), 3.93 (s, 3H (minor isomer)), 6.74 – 6.76 (m, 1H), 6.92 – 6.98 (m, 2H), 7.04 – 7.09 (m, 1H), 7.43 – 7.45 (m, 3H), 7.92 – 7.95 (m, 2H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) 14.6, 15.0, 20.9, 21.8, 33.8, 44.0, 56.5, 111.8, 112.3, 121.1, 121.4, 121.7, 122.1, 124.8, 127.1, 127.8, 128.6, 129.2, 131.1, 139.4, 141.5, 149.7, 172.1 ppm; HRMS Calcd. for C$_{17}$H$_{19}$NO (M+1) 254.15394, found 254.15384.

$N$-(hexan-2-ylidene)-2-methoxyaniline (25)

Yellow liquid, 35% yield, mixture of isomers 3.9:1; $^1$H NMR (400 MHz, CDCl$_3$) 0.79 (minor isomer, t, $J = 7.24$ Hz, 3H), 0.96 (major isomer, t, $J = 7.21$ Hz, 3H), 1.19 (minor isomer, sextet, $J = 7.20$ Hz, 2H), 1.43 (major isomer, sextet, $J = 7.37$ Hz, 2H), 1.67 (major isomer, quintet, $J = 7.37$ Hz, 2H), 1.72 (s, 3H), 2.06 (minor isomer, t, $J = 8.09$ Hz, 2H), 2.19 (minor
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isomer, s, 3H), 2.45 (t, $J = 7.30$ Hz, 2H), 3.76 (s, 3H), 6.61 – 6.67 (m, 1H), 6.84 – 7.05 (m, 3H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) 14.7, 14.9, 20.6, 23.3, 23.5, 26.8, 29.6, 35.3, 42.4, 56.3, 56.4, 111.9, 112.3, 121.5, 121.6, 121.7, 124.7, 140.9, 141.4, 150.1, 174.8, 175.2 ppm; HRMS Calcd. for C$_{13}$H$_{19}$NO (M+1) 205.1467, found 205.1464.

**2-methoxy-N-(octan-2-ylidene)aniline (26)**

![Structure of 2-methoxy-N-(octan-2-ylidene)aniline (26)]

Light yellow liquid, 40% yield, mixture of isomers 3.3:1; $^1$H NMR (400 MHz, CDCl$_3$) 0.82 (minor isomer, t, $J = 7.11$ Hz, 3H), 0.89 (major isomer, t, $J = 6.90$ Hz, 3H), 1.12 – 1.23 (major isomer, m, 2H), 1.30 – 1.42 (major isomer, m, 6H), 1.63 – 1.68 (minor isomer, m, 2H), 1.71 (s, 3H), 2.05 (minor isomer, t, $J = 8.04$ Hz, 2H), 2.18 (minor isomer, s, 3H), 2.44 (major isomer, t, $J = 7.85$ Hz, 2H), 3.75 (s, 3H), 6.62 – 6.66 (m, 1H), 6.85 – 6.90 (m, 2H), 6.97 – 7.03 (m, 1H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) 14.9, 15.0, 20.5, 23.3, 23.5, 26.7, 27.3, 27.4, 29.8, 30.0, 32.3, 32.6, 35.5, 42.6, 56.4, 111.9, 112.2, 121.4, 121.5, 121.6, 124.6, 124.7, 140.9, 141.4, 150.1, 174.7, 175.2 ppm.

**Benzyl-(1-phenyl-ethylidene)-amine (27)**[7]3

![Structure of Benzyl-(1-phenyl-ethylidene)-amine (27)]

Colourless oil, solidifies slowly, 58% yield; $^1$H NMR (400 MHz, CDCl$_3$) 2.35 (s, 3H), 4.76 (s, 2H), 7.26 – 7.45 (m, 8H), 7.85 – 7.95 (m, 2H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) 15.8, 55.6, 126.5, 126.6, 127.7, 128.2, 128.3, 129.5, 140.5, 141.1, 165.9 ppm.
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\( N\)-(1-phenylethylidene)butan-1-amine (28)\(^{72} \)

![Chemical structure of (1-phenylethylidene)butan-1-amine (28)]

Colourless oil, 69% yield, mixture of isomers 3.3:1; \(^1\)H NMR (400 MHz, CDCl\(_3\)) 0.88 (minor isomer, t, \( J = 7.31 \) Hz, 3H), 1.01 (major isomer, t, \( J = 7.31 \) Hz, 3H), 1.3 (minor isomer, sextet, \( J = 7.71 \) Hz, 2H), 1.49 (major isomer, sextet, \( J = 7.60 \) Hz, 2H), 2.24 (s, 3H), 3.49 (t, \( J = 7.12 \) Hz, 2H), 7.37 – 7.39 (m, 3H), 7.77 – 7.81 (m, 2H) ppm; \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) 15.0, 21.7, 34.0, 52.9, 127.4, 129.1, 130.1, 142.4, 165.6 ppm.

\( N\)-(2,3-dihydro-1H-inden-1-ylidene)butan-1-amine (29)

![Chemical structure of (2,3-dihydro-1H-inden-1-ylidene)butan-1-amine (29)]

Colourless oil, 31% yield; \(^1\)H NMR (400 MHz, CDCl\(_3\)) 0.97 (t, \( J = 7.35 \) Hz, 3H), 1.44 (sextet, \( J = 6.44 \) Hz, 2H), 1.72 (quintet, \( J = 7.20 \) Hz, 2H), 2.69 (t, \( J = 6.45 \) Hz, 2H), 3.06 (t, \( J = 6.07 \) Hz, 2H), 3.46 (t, \( J = 7.24 \) Hz, 2H), 7.25 – 7.38 (m, 3H), 7.82 (d, \( J = 7.56 \) Hz, 1H) ppm; \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) 15.0, 21.8, 28.8, 29.0, 54.6, 123.1, 126.4, 127.7, 131.7, 140.8, 150.3, 174.5 ppm; HRMS Calcd. for C\(_{13}\)H\(_{17}\)N (M+1) 188.14338, found 188.14279.

\((R\)-\(N\)-Phenyl-1-phenyl-ethylamine (10a)\(^{25,29,74} \)

![Chemical structure of (R)-N-Phenyl-1-phenyl-ethylamine (10a)]

Yellow oil, 95% yield, 87% ee, \([\alpha]_D = -4.5 \) (c 1.05, CHCl\(_3\)), lit. value\(^{25} 84\%\) ee, \([\alpha]_D = -3.9 \) (c 1.00, CHCl\(_3\)); \(^1\)H NMR (400 MHz, CDCl\(_3\)) 1.53 (d, \( J = 6.7 \) Hz, 3H), 3.98 (br, 1H), 4.50 (q, \( J = 6.7 \), 1H), 6.52 (d, \( J = 7.6 \) Hz, 2H), 6.66 (t, \( J = 7.33 \) Hz, 1H), 7.09 – 7.13 (m, 2H), 7.22 – 7.26 (m, 1H), 7.31 – 7.40 (m, 4H) ppm; \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) 25.9, 54.4, 114.2, 118.1, 126.8, 127.8, 129.6, 130.0, 146.2, 148.2 ppm; HRMS Calcd. for C\(_{14}\)H\(_{15}\)N (M+1)
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197.1204, found 197.1196, GC Chiralsil DEX CB, (initial temp. 100 °C for 5 min, then 5 °C/min to 160 °C, then 10 °C/min to 170 °C, then 10 °C/min to 100 °C), t1 = 31.5 min, t2 = 34.3 min.

(R)-N-(4-Methoxy-phenyl)-1-phenyl-ethylamine (11a)\textsuperscript{25,29,34}

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

Yellow solid, 92% yield, Mp = 63.8 – 63.9 °C, 71% ee, [\(\alpha\)]\textsubscript{D} = +1.4 (c 1.00, CHCl\textsubscript{3}), lit. value\textsuperscript{25} 88% ee, [\(\alpha\)]\textsubscript{D} = +1.3 (c 1.00, CHCl\textsubscript{3}); \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) 1.50 (d, \(J = 6.7\) Hz, 3H), 3.86 (br, 1H), 3.70 (s, 3H), 4.42 (q, \(J = 6.7\) Hz, 1H), 6.47 – 6.49 (m, 2H), 6.69 – 6.71 (m, 2H), 7.22 – 7.24 (m, 1H), 7.30 – 7.38 (m, 4H) ppm; \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) 26.0, 55.1, 56.6, 115.4, 115.6, 126.8, 127.7, 129.5, 142.5, 146.4, 152.8 ppm; HRMS Calcd. for C\textsubscript{15}H\textsubscript{17}NO (M+1) 227.1310, found 227.1300; HPLC (OD-H, eluent:heptane/i-PrOH = 99/1, detector: 215 nm, flow rate: 0.5 mL/min), t1 = 26.2 min, t2 = 28.5 min.

(R)-N-(2-Methoxy-phenyl)-1-phenyl-ethylamine (12a)\textsuperscript{75}

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

Light brown solid, 93% yield, Mp = 71.4 °C, 97% ee, [\(\alpha\)]\textsubscript{D} = -32.3 (c 1.03, CHCl\textsubscript{3}), absolute configuration was determined by measuring the optical rotation of deprotected derivatized product 12c and comparing it with literature data\textsuperscript{76}; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) 1.71 (d, \(J = 6.7\) Hz, 3H), 4.02 (s, 3H), 4.65 (q, \(J = 6.7\) Hz, 1H), 4.83 (br, 1H), 6.54 (d, \(J = 7.8\) Hz, 1H), 6.78 – 6.81 (m, 1H), 6.87 – 6.94 (m, 2H), 7.36 – 7.40 (m, 1H), 7.46 – 7.50 (m, 2H), 7.54 – 7.56 (m, 2H) ppm; \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) 26.0, 54.1, 56.2, 110.1, 111.9, 117.2, 122.0, 126.7, 127.6, 129.4, 138.0, 146.3, 147.4 ppm; HRMS Calcd. for C\textsubscript{15}H\textsubscript{17}NO (M+1) 227.1310, found 227.1302; HPLC
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(OD-H, eluent: heptane/i-PrOH = 99/1, detector: 215 nm, flow rate: 0.5 mL/min), t₁ = 14.6 min, t₂ = 19.0 min.

(R)-N-(1-Phenyl-ethyl)amine hydrochloride (12b)

\[
\text{NH}_2\text{HCl}
\]

Light brown solid, 70% yield, Mp = 142.5 – 142.7 °C; \(^1\)H NMR (400 MHz, D₂O) 1.64 (d, \(J = 6.91\) Hz, 3H), 4.53 (q, \(J = 6.86\) Hz, 1H), 7.47 – 7.52 (m, 5H) ppm; \(^{13}\)C NMR (100 MHz, D₂O) 19.5, 51.2, 126.7, 129.3, 129.4, 137.9 ppm; HRMS Calcd. for C₈H₁₂ClN (M+1–HCl) 122.09643, found 122.09645; product was derivatized with acetic anhydride in the presence of triethylamine and the ee of the N-Ac derivative 12c was determined by GC.

(R)-N-(1-Phenyl-ethyl)-acetamide (12c)

\[
\text{NHAc}
\]

Light brown solid, 97% ee; \(^1\)H NMR (400 MHz, CDCl₃) 1.47 (d, \(J = 6.91\) Hz, 3H), 1.97 (s, 3H), 5.13 (q, \(J = 7.20\) Hz, 1H), 5.88 (br, 1H), 7.26 – 7.34 (m, 5H) ppm; \(^{13}\)C NMR (100 MHz, CDCl₃) 22.6, 24.4, 49.7, 127.2, 128.3, 129.6, 144.1, 170.1 ppm; GC Chiralsil DEX CB, initial temp. 125 °C for 4 min, then 3 °C/min to 140 °C, then 10 °C/min to 180 °C, then 10 °C/min to 125 °C), t₁ = 13.0 min, t₂ = 13.25 min.

(R)-N-(3,5-Dimethyl-phenyl)-(1-phenyl-ethyl)-amine (13a)

\[
\text{NH}
\]

Yellow oil, 97% yield, >99% ee, \([\alpha]_D^0 = +12.3\) (c 1.02, CHCl₃); \(^1\)H NMR (400 MHz, CDCl₃) 1.62 (d, \(J = 6.7\) Hz, 3H), 2.32 (s, 6H), 4.02 (br, 1H), 4.61 (q, \(J = 6.7\) Hz, 1H), 6.31 (s, 2H), 6.47(s, 1H), 7.34 – 7.37 (m, 1H), 7.43 – 7.47 (m, 2H), 7.50 – 7.52 (m, 2H) ppm; \(^{13}\)C NMR (100 MHz, CDCl₃) 22.4, 25.8, 54.2,
In a HTE experiment with MAO conversion was determined by GC:

Agilent HP-5, initial temp. 80°C for 2min, then 15°C/min to 280°C, hold 4 min, retention times: starting imine t = 11.9 min, product t = 11.5 min.

\((-\)\)-\(N\)-(1-Phenyl-ethyl)-3,4,5-trimethoxy-phenyl-amine (14a)

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

Yellow oil, 94% yield, 99% ee, \([\alpha]_D = -21.0 (c 1.09, \text{CHCl}_3)\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) 1.51 (d, \(J = 6.7\) Hz, 3H), 3.68 (s, 6H), 3.74 (s, 3H), 4.09 (br, 1H), 4.44 (q, \(J = 6.7\) Hz, 1H), 5.77 (s, 2H), 7.21 – 7.25 (m, 1H), 7.31 – 7.40 (m, 2H) ppm; \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) 25.7, 54.8, 56.4, 61.7, 91.7, 126.5, 127.6, 129.4, 130.4, 144.9, 146.2, 154.4 ppm; HRMS Calcd. for C\(_{17}\)H\(_{21}\)NO\(_3\) (M+1) 287.1521, found 287.1516; HPLC (AD, eluent:heptane/i-PrOH = 90/10, detector: 215 nm, flow rate: 0.5 mL/min), \(t_1 = 11.1\) min, \(t_2 = 23.8\) min.

\((+\)\)-\(N\)-(4-Methoxy-3,5-dimethyl-phenyl)-1-phenyl-ethylamine (15a)

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

Light yellow solid, 96% yield, Mp = 90.2 – 90.9 °C, 99% ee, \([\alpha]_D = +9.0 (c 1.02, \text{CHCl}_3)\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) 1.52 (d, \(J = 6.7\) Hz, 3H), 2.20 (s, 6H), 3.66 (s, 3H), 3.81 (br, 1H), 4.46 (q, \(J = 6.7\) Hz, 1H), 6.23 (s, 2H), 7.25 – 7.29 (m, 1H), 7.34 – 7.43 (m, 4H) ppm; \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) 17.1, 25.8, 54.6, 60.7, 114.2, 126.7, 127.6, 129.4, 132.0, 144.3, 146.4, 149.6
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ppm; HRMS Calcd. for C₁₇H₂₁NO (M+1) 255.1623, found 255.1630; HPLC (OD-H, eluent: heptane/i-PrOH = 80/20, detector: 215 nm, flow rate: 0.5 mL/min), t₁ = 9.2 min, t₂ = 9.9 min.

(R)-N-(2-Methoxy-phenyl)-1-naphthalen-2-yl-ethylamine (16a)

White solid, 93% yield, Mp = 110.5 – 111.2 °C, 99% ee, [α]₀ = -76.8 (c 1.04, CHCl₃), absolute configuration was determined by measuring the optical rotation of deprotected derivatized product 16c and comparing it with literature data; ¹H NMR (400 MHz, CDCl₃) 1.70 (d, J = 6.7 Hz, 3H), 3.97 (s, 3H), 4.70 (q, J = 6.7 Hz, 1H), 4.82 (br, 1H), 6.45–6.50 (m, 1H), 6.64 – 6.88 (m, 3H), 7.48 – 7.61 (m, 3H), 7.89 – 7.91 (m, 4H) ppm; ¹³C NMR (100 MHz, CDCl₃) 26.1, 54.6, 56.4, 110.2, 112.1, 117.3, 122.1, 125.2, 125.4, 126.4, 126.9, 128.6, 128.8, 129.4, 133.7, 134.5, 138.2, 143.9, 147.5 ppm; HRMS Calcd. for C₁₉H₁₉NO (M+1) 277.1467, found 277.1476. HPLC (OD-H, eluent: heptane/i-PrOH = 99/1, detector: 215 nm, flow rate: 0.5 mL/min), t₁ = 19.5 min, t₂ = 24.7 min.

(R)-1-Naphthalen-2-yl-ethylamine hydrochloride (16b)

Light brown solid, 68% yield, Mp = 214.6 – 214.7 °C; ¹H NMR (400 MHz, D₂O) 1.47 (d, J = 6.49 Hz, 3H), 4.41 (q, J = 6.44 Hz, 1H), 7.28 – 7.30 (m, 3H), 7.57 – 7.65 (m, 4H) ppm; ¹³C NMR (100 MHz, D₂O) 19.4, 51.2, 123.9, 125.9, 127.0, 127.1, 127.8, 128.1, 129.2, 132.9, 133.1, 135.2 ppm; HRMS Calcd. for C₁₂H₁₄ClN (M+1-HCl) 172.1108, found 172.11195; the product was derivatized with acetic anhydride in the presence of triethylamine and the ee of the N-Ac derivative 16c was determined by GC:
White solid, Mp = 119.2 – 119.3 °C, >99% ee, $\alpha_D = +23.6$ (c 1.00, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) 1.54 (d, $J = 6.93$ Hz, 3H), 1.97 (s, 3H), 5.26 (q, $J = 7.24$ Hz, 1H), 6.21 (br, 1H), 7.40 – 7.47 (m, 3H), 7.74 – 7.80 (m, 4H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) 22.6, 24.4, 49.8, 125.5, 125.7, 126.8, 127.2, 128.6, 128.8, 129.4, 133.7, 134.3, 141.5, 170.1 ppm; HRMS Calcd. for C$_{14}$H$_{15}$NO (M+1) 214.12264, found 214.12283; GC Chiralsil DEX CB, initial temp. 125 °C for 4 min, then 3 °C/min to 140 °C, then 10 °C/min to 180 °C, then 10 °C/min to 125 °C, $t_1 = 37.8$ min, $t_2 = 38.57$ min.

Light yellow solid, 95% yield, Mp = 88.6 – 88.8 °C, 98% ee, $\alpha_D = -19.1$ (c 1.00, CHCl$_3$); $^1$H NMR (400 MHz, CDCl$_3$) 1.54 (d, $J = 6.7$ Hz, 3H), 2.32 (s, 3H), 3.88 (s, 3H), 4.45 (q, $J = 6.5$ Hz, 1H), 4.60 (br, 1H), 6.33 – 6.38 (m, 1H), 6.55 – 6.79 (m, 3H), 7.10 – 7.14 (m, 2H), 7.24 – 7.28 (m, 2H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) 22.0, 26.1, 53.9, 56.3, 110.1, 111.9, 117.1, 122.1, 126.7, 130.2, 137.2, 138.2, 143.4, 147.4 ppm; HRMS Calcd. for C$_{16}$H$_{19}$NO (M+1) 241.1467, found 241.1458; HPLC (OD-H, eluent:heptane/i-PrOH = 99/1, detector: 215 nm, flow rate: 0.5 mL/min), $t_1 = 12.9$ min, $t_2 = 15.4$ min.

Light brown solid, 71% yield; $^1$H NMR (400 MHz, D$_2$O) 1.47 (d, $J = 6.85$ Hz, 3H), 2.19 (s, 3H), 4.35 (q, $J = 6.74$ Hz, 1H), 7.15 – 7.22 (m, 4H) ppm; $^{13}$C
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NMR (100 MHz, D2O) 19.5, 20.4, 51.0, 126.7, 130.0, 134.9, 139.7 ppm; HRMS Calcd. for C9H14ClN (M+1–HCl) 136.11208, found 136.11205; the product was derivatized (in the GC vial) with acetic anhydride in the presence of triethylamine and the ee of the N-Ac derivative 17c was determined by GC.

(1-p-Tolyl-ethyl)-acetamide (17c)

\[
\text{NHAc}
\]

98% ee, GC Chiralsil DEX CB, initial temp. 125 °C for 4 min, then 3 °C/min to 140 °C, then 10 °C/min to 180 °C, then 10 °C/min to 125 °C, \( t_1 = 14.7 \) min, \( t_2 = 15.0 \) min.

(--)-N-[1-(4-Chloro-phenyl)-ethyl]-[2-methoxy-phenyl]-amine (18a)

\[
\text{Cl}
\]

Light brown solid, 95% yield, Mp = 113.3 – 114.1 °C, 96% ee, [\( \alpha \)]D = -34.8 (c 1.01, CHCl3); \(^1\)H NMR (400 MHz, CDCl3) 1.53 (d, \( J = 6.7 \) Hz, 3H), 3.89 (s, 3H), 4.45 (q, 1H), 4.61 (br, 1H), 6.26 – 6.28 (m, 1H), 6.60 – 6.79 (m, 3H), 7.26 – 7.32 (m, 4H) ppm; \(^13\)C NMR (100 MHz, CDCl3) 25.4, 53.1, 55.6, 109.5, 111.2, 116.8, 121.3, 127.5, 129.0, 132.5, 137.2, 144.3, 146.8 ppm; HRMS Calcd. for C15H16ClNO (M+1) 261.0920, found 261.0915; HPLC (OD-H, eluent:heptane/i-ProOH = 99/1, detector: 215 nm, flow rate: 0.5 mL/min), \( t_1 = 16.4 \) min, \( t_2 = 22.7 \) min.
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(−)-N-(2-Methoxy-phenyl)-1-(4-trifluoromethyl-phenyl)-ethylamine (19a)

\[
\text{\begin{align*}
\text{\text{H}} & \quad \text{\text{O}} \\
\text{\text{O}} & \quad \text{\text{H}} \\
\text{\text{F}_3\text{C}} & \quad \text{\text{H}} \\
\end{align*}}
\]

White solid, 97% yield, Mp = 93.7 – 93.8 °C, 97% ee, [α]D = -40.8 (c 1.01, CHCl₃); \(^1\)H NMR (400 MHz, CDCl₃) 1.56 (d, \(J = 6.7\) Hz, 3H), 3.91 (s, 3H), 4.53, (q, \(J = 6.2\) Hz, 1H), 4.66 (br, 1H), 6.24 – 6.26 (m, 1H), 6.63 – 6.72 (m, 2H), 6.78 – 6.80 (m, 1H), 7.48–7.50 (m, 2H), ppm; \(^{13}\)C NMR (100 MHz, CDCl₃) 26.0, 54.1, 56.3, 110.3, 111.9, 117.7, 122.0, 125.3 (q, \(J = 271.9\) Hz), 126.5 (q, \(J = 3.8\) Hz), 127.1, 130.0 (q, \(J = 32.2\) Hz), 137.7, 147.5, 150.7 ppm; \(^{19}\)F (376 MHz, CDCl₃) -62.7 ppm; HRMS Calcd. for C₁₆H₁₆F₃NO (M+1) 295.1184, found 295.1171; HPLC (OD-H, eluent:heptane/i-PrOH = 99/1, detector: 215 nm, flow rate: 0.5 mL/min), \(t_1 = 16.2\) min, \(t_2 = 24.2\) min.

(−)-N-[1-(4-Fluoro-phenyl)-ethyl]-[2-methoxy-phenyl]-amine (20a)

\[
\text{\begin{align*}
\text{\text{H}} & \quad \text{\text{O}} \\
\text{\text{O}} & \quad \text{\text{H}} \\
\text{\text{F}} & \quad \text{\text{H}} \\
\end{align*}}
\]

White solid, 94% yield, Mp = 71.0 – 72.1 °C, 97% ee, [α]D = -56.0 (c 1.00, CHCl₃); \(^1\)H NMR (400 MHz, CDCl₃) 1.68 (d, \(J = 6.7\) Hz, 3H), 4.01 (s, 3H), 4.62 (q, \(J = 6.7\) Hz, 1H), 4.82 (br, 1H), 6.50 – 6.52 (m, 1H), 6.79 – 6.84 (m, 1H), 6.88 – 6.95 (m, 2H), 7.13 – 7.17 (m, 2H), 7.47 – 7.50 (m, 2H) ppm; \(^{13}\)C NMR (100 MHz, CDCl₃) 25.6, 53.0, 55.7, 109.5, 111.3, 115.6 (d, \(J = 21.3\) Hz), 116.8, 121.4, 127.5 (d, \(J = 7.9\) Hz), 137.3, 141.3 (d, \(J = 3.0\) Hz), 146.8, 162.0 (d, \(J = 244.1\) Hz) ppm; \(^{19}\)F (376 MHz, CDCl₃) -116.9 ppm; HRMS Calcd. for C₁₅H₁₅FNO (M+1) 243.1059, found 243.1048; HPLC (OD-H, eluent:heptane/i-PrOH = 99/1, detector: 215 nm, flow rate: 0.5 mL/min), \(t_1 = 15.3\) min, \(t_2 = 20.3\) min.
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\(-\)-N-(2-Methoxy-phenyl)-1-m-tolyl-ethylamine (21a)

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

Colourless oil, 88% yield, 93% ee, \([\alpha]_D = -16.9 \ (c 1.00, \text{CHCl}_3)\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) 1.54 (d, \(J = 6.7 \text{ Hz, 3H}\), 2.34 (s, 3H), 3.89 (s, 3H), 4.43 (q, \(J = 6.7 \text{ Hz, 1H}\), 4.61 (br, 1H), 6.34 – 6.39 (m, 1H), 6.57 – 6.80 (m, 3H), 7.02 – 7.05 (m, 1H), 7.18 – 7.26 (m, 3H) ppm; \(^1^3\)C NMR (100 MHz, CDCl\(_3\)) 22.4, 26.1, 54.3, 56.2, 110.1, 111.9, 117.1, 122.1, 123.8, 127.4, 128.5, 129.4, 138.2, 139.0, 146.4, 147.4 ppm; HRMS Calcd. for C\(_{16}\)H\(_{19}\)NO (M+1) 241.1467, found 241.1452; HPLC (OD-H, eluent:heptane/i-PrOH = 99/1, detector: 215 nm, flow rate: 0.5 mL/min), \(t_1 = 12.8 \text{ min}, t_2 = 15.8 \text{ min}\).

\(-\)-N-(2-Methoxy-phenyl)-1-(3-nitro-phenyl)-ethylamine (22a)

\[
\begin{align*}
\text{HN} & \quad \text{O}_2\text{N} \\
\text{HN} & \quad \text{O}_2\text{N}
\end{align*}
\]

Yellow solid, 95% yield, 61% ee, Mp = 78.9 – 79.6 \({^\circ}\text{C}\), \([\alpha]_D = -41.7 \ (c 1.02, \text{CHCl}_3)\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) 1.61 (d, \(J = 6.75 \text{ Hz, 3H}\), 3.93 (s, 3H), 4.59 (q, \(J = 6.70 \text{ Hz, 1H}\), 4.76 (br, 1H), 6.25 – 6.28 (m, 1H), 6.65 – 6.75 (m, 2H), 6.81 – 6.84 (m, 1H), 7.49 (t, \(J = 7.9 \text{ Hz, 1H}\), 7.73 – 7.76 (m, 1H), 8.08 – 8.11 (m, 1H), 8.28 – 8.29 (m, 1H) ppm; \(^1^3\)C NMR (100 MHz, CDCl\(_3\)) 26.0, 53.9, 56.3, 110.3, 111.7, 117.9, 121.8, 121.9, 122.9, 130.5, 133.0, 137.4, 147.5, 149.0, 149.5 ppm; HRMS Calcd. for C\(_{15}\)H\(_{16}\)N\(_2\)O\(_3\) (M+1) 273.12337, found 273.12329; HPLC (OD-H, eluent:heptane/i-PrOH = 80/20, detector: 215 nm, flow rate: 0.5 mL/min), \(t_1 = 12.6 \text{ min}, t_2 = 16.8 \text{ min}\).
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(–)-\(N\)-(2-Methoxy-phenyl)-1-phenyl-propylamine (23a)

\[
\begin{array}{c}
\text{HN} \\
\text{O} \\
\text{Ph} \\
\text{Ph} \end{array}
\]

Yellow oil, 96% yield, 94% ee, \([\alpha]_D = -13.7\) (c 1.00, CHCl\(_3\)); \(^1\)H NMR (400 MHz, CDCl\(_3\)) 1.06 (t, J = 7.44 Hz, 3H), 1.94 (quint, J = 7.05 Hz, 2H), 3.95 (s, 3H), 4.30 (br, 1H), 4.78 (br, 1H), 6.43 – 6.45 (m, 1H), 6.67 – 6.69 (m, 1H), 6.76 – 6.84 (m, 2H), 7.29 – 7.31 (m, 1H), 7.38 – 7.42 (m, 4H) ppm; \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) 11.7, 32.6, 56.2, 60.4, 110.1, 111.7, 117.0, 122.0, 127.3, 127.6, 129.3, 138.3, 145.0, 147.5 ppm; HRMS Calcd. for C\(_{16}\)H\(_{19}\)NO (M+1) 241.1467, found 241.1469; HPLC (OD-H, eluent:heptane/i-PrOH = 99/1, detector: 215 nm, flow rate: 0.5 mL/min), \(t_1 = 13.0\) min, \(t_2 = 15.1\) min.

(–)-\(N\)-(2-Methoxy-phenyl)-(1-phenyl-butyl)-amine (24a)

\[
\begin{array}{c}
\text{HN} \\
\text{O} \\
\text{Ph} \\
\text{Ph} \end{array}
\]

Colourless oil, 96% yield, 97% ee, \([\alpha]_D = -23.6\) (c 1.03, CHCl\(_3\)); \(^1\)H NMR (400 MHz, CDCl\(_3\)) 0.96 (t, J = 7.35 Hz, 3H), 1.35 – 1.53 (m, 2H), 1.78 – 1.88 (m, 2H), 3.90 (s, 3H), 4.31 (t, J = 6.86 Hz, 1H), 4.70 (br, 1H), 6.35 – 6.37 (m, 1H), 6.58 – 6.62 (m, 1H) 6.68 – 6.78 (m, 2H), 7.20 – 7.26 (m, 1H), 7.30 – 7.37 (m, 4H) ppm; \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) 15.0, 20.6, 42.2, 56.4, 58.8, 110.29, 111.8, 117.0, 122.1, 127.3, 127.7, 129.4, 138.4, 145.5, 147.5 ppm; HRMS Calcd. for C\(_{17}\)H\(_{21}\)NO (M+1) 256.16959, found 256.16949; HPLC (OD-H, eluent:heptane/i-PrOH = 99/1, detector: 215 nm, flow rate: 0.5 mL/min), \(t_1 = 12.1\) min, \(t_2 = 17.9\) min.
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N-(hexan-2-yl)-2-methoxyaniline (25a)

\[
\text{HN} \hspace{1cm} \text{O} \hspace{1cm} \text{NH}_2
\]

Light yellow liquid, 96% yield, 16% ee; \(^1\)H NMR (400 MHz, CDCl\(_3\)) 0.93 (t, \(J = 6.72\) Hz, 3H), 1.20 – 1.70 (m, 9H), 3.48 (q, \(J = 6.03\) Hz, 1H), 3.86 (s, 3H), 4.06 (br, 1H), 6.60 – 6.68 (m, 2H), 6.77 – 6.89 (m, 2H) ppm; \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) 15.1, 21.8, 23.8, 29.4, 37.9, 49.0, 56.3, 110.4, 110.9, 116.5, 122.2, 138.6, 147.6 ppm; HRMS Calcd. for C\(_{13}\)H\(_{21}\)NO (M+1) 207.1623, found 207.1620; HPLC (OD-H, eluent:heptane/\(i\)-PrOH = 99/1, detector: 215 nm, flow rate: 0.5 mL/min), \(t_1 = 10.2\) min, \(t_2 = 12.1\) min.

2-methoxy-N-(octan-2-yl)aniline (26a)

\[
\text{HN} \hspace{1cm} \text{O} \hspace{1cm} \text{NH}_2
\]

Light yellow liquid, 95% yield, 17% ee; \(^1\)H NMR (400 MHz, CDCl\(_3\)) 1.01 (t, \(J = 6.80\) Hz, 3H), 1.30 (d, \(J = 6.28\) Hz, 3H), 1.41 – 1.60 (m, 9H), 1.68 – 1.76 (m, 1H), 3.56 (q, \(J = 6.02\) Hz, 1H), 3.92 (s, 3H), 4.18 (br, 1H), 6.69 – 6.76 (m, 2H), 6.85 – 6.87 (m, 1H), 6.94 – 7.0 (m, 1H) ppm; \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) 15.01, 21.7, 23.6, 27.1, 30.3, 32.8, 38.1, 49.0, 56.2, 110.3, 110.9, 116.5, 122.2, 138.5, 147.6 ppm; HPLC (OD-H, eluent:heptane/\(i\)-PrOH = 99/1, detector: 215 nm, flow rate: 0.5 mL/min), \(t_1 = 10.4\) min, \(t_2 = 13.6\) min.

Benzyl-(1-phenyl-ethyl)-amine (27a)

\[
\text{HN} \hspace{1cm} \text{O} \hspace{1cm} \text{NH}_2
\]

Pale yellow oil; \(^1\)H NMR (400 MHz, CDCl\(_3\)) 1.37 (d, \(J = 6.60\) Hz, 3H), 1.63 (br, 1H), 3.60 (d, \(J = 13.10\) Hz, 1H), 3.67 (d, \(J = 13.10\) Hz, 1H), 3.82 (q, \(J = 6.60\) Hz, 1H), 7.26 – 7.37 (m, 10H) ppm; \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) 24.5, 51.6, 57.5, 126.7, 126.8, 126.9, 128.1, 128.3, 128.5, 140.6, 145.5 ppm;
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HPLC (OD-H, eluent:heptane/i-PrOH = 99/1, detector: 215 nm, flow rate: 0.5 mL/min), \( t_1 = 11.1 \) min, \( t_2 = 12.3 \) min.

\( N\)-(1-phenylethyl)butan-1-amine (28a)\)

\[
\begin{align*}
& \text{Colourless oil; } ^1H \text{ NMR (400 MHz, CDCl}_3\text{) 0.89 (t, } J = 7.30 \text{ Hz, 3H), 1.29} - 1.37 \text{ (m, 5H), 1.43} - 1.50 \text{ (m, 2H), 2.40} - 2.55 \text{ (m, 2H), 3.76 (q, } J = 6.45 \text{ Hz, 1H), 7.22} - 7.33 \text{ (m, 5H) ppm; } ^{13}C \text{ NMR (100 MHz, CDCl}_3\text{) 14.9, 21.4,} \\
& \text{25.3, 33.4, 48.5, 59.3, 127.4, 127.7, 129.3, 146.8 ppm; HPLC (AS-H, eluent:heptane/i-PrOH = 99.7/0.3, detector: 215 nm, flow rate: 0.5 mL/min), } t_1 = 9.3 \text{ min, } t_2 = 10.1 \text{ min.}
\end{align*}
\]

\( N\)-butyl-2,3-dihydro-\( 1H \)-inden-1-amine (29a)\)

\[
\begin{align*}
& \text{Orange oil; } ^1H \text{ NMR (400 MHz, CDCl}_3\text{) 0.98 (t, } J = 7.37 \text{ Hz, 3H), 1.39} \\
& \text{(sextet, } J = 7.37 \text{ Hz, 2H), 1.52 (quintet, } J = 6.95 \text{ Hz, 2H), 1.80} - 1.89 \text{ (m, 2H), 2.38} - 2.46 \text{ (m, 1H), 2.74 (t, } J = 7.37 \text{ Hz, 2H), 2.78} - 2.86 \text{ (m, 1H),} \\
& \text{2.98} - 3.05 \text{ (m, 1H), 4.26 (t, } J = 6.57 \text{ Hz, 1H), 7.19} - 7.26 \text{ (m, 3H), 7.35} - 7.37 \text{ (m, 1H) ppm; } ^{13}C \text{ NMR (100 MHz, CDCl}_3\text{) 15.0, 21.5, 31.3, 33.6, 34.6,} \\
& \text{48.1, 64.3, 125.0, 125.7, 127.1, 128.2, 144.5, 146.4 ppm; HRMS Calcd. for C_{13}H_{19}N (M+1) 190.15903, found 190.15839; HPLC (AS-H, eluent:heptane/i-PrOH = 99.7/0.3, detector: 210 nm, flow rate: 0.5 mL/min), } t_1 = 8.7 \text{ min, } t_2 = 9.7 \text{ min.}
\end{align*}
\]

6,7-dimethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline (30a)\)

\[
\begin{align*}
& \text{White solid, 98\% yield, Mp = 97.3} - 97.9 \text{ °C; } ^1H \text{ NMR (400 MHz, CDCl}_3\text{) 1.41 (d, } J = 6.28 \text{ Hz, 3H), 2.61} - 2.65 \text{ (m, 1H), 2.75} - 2.80 \text{ (m, 2H), 2.94} - 2.99 \text{ (m, 1H), 3.21} - 3.24 \text{ (m, 1H), 3.81 (s, 6H), 4.03 (br, 1H), 6.53 (s, 1H),}
\end{align*}
\]

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6.58 (s, 1H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) 23.6, 30.2, 42.5, 52.0, 56.7, 56.9, 109.9, 112.6, 127.5, 133.0, 148.2, 148.3 ppm; HPLC (OD-H, eluent: heptane/ $i$-PrOH = 88/12, detector: 215 nm, flow rate: 0.5 mL/min), t$_1$ = 23.5 min, t$_2$ = 28.3 min.

In a HTE experiment with MAO conversion was determined by HPLC:

Response factor was calculated: starting amine: Rf (Area/mg) = 40586, product: Rf (Area/mg) = 3407, column: Chiralpak OD-H, eluent: 95% n-heptane/5% IPA/0.05% DEA, flow: 1.3 mL/min, temperature: 50°C, wavelength: 254 nm, inject. Volume: 5µl, run time: 20 min, retention time: Starting imine t = 7.3 min, product t$_1$ = 10.4 and t$_2$ = 12.0 min.

6,7-diethoxy-1-methyl-1,2,3,4-tetrahydroisoquinoline (31a)

Light yellow solid, 97% yield, Mp = 63.9 – 64.0 °C; $^1$H NMR (400 MHz, CDCl$_3$) 1.38 – 1.44 (m, 9H), 1.68 (br, 1H), 2.58 – 2.65 (m, 1H), 2.72 – 2.80 (m, 1H), 2.95 – 3.01 (m, 1H), 3.20 – 3.26 (m, 1H), 3.77 (br, 1H), 4.05 (q, $J$ = 6.99 Hz, 1H), 6.57 (s, 1H), 6.64 (s, 1H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) 15.4, 15.5, 23.3, 30.0, 42.5, 51.7, 65.0, 65.4, 112.4, 114.6, 127.7, 133.2, 147.4, 147.8 ppm; HPLC (OD-H, eluent: heptane/ $i$-PrOH = 88/12, detector: 215 nm, flow rate: 0.5 mL/min), t$_1$ = 18.0 min, t$_2$ = 25.4 min.

2,3,3-trimethylindoline (33a)$^{82}$

$^1$H NMR (400 MHz, CDCl$_3$) 1.05 (s, 3H), 1.19 (d, $J$ = 6.56 Hz, 3H), 1.29 (s, 3H), 3.52 (q, $J$ = 6.55 Hz, 1H), 6.62 – 6.64 (m, 1H), 6.73 – 6.77 (m, 1H), 7.01 – 7.05 (m, 2H) ppm; $^{13}$C NMR (100 MHz, CDCl$_3$) 16.1, 23.3, 27.1, 44.3, 66.1, 110.3, 119.8, 123.2, 128.1, 140.1, 150.2 ppm; HPLC (OJ-H, eluent: heptane/ $i$-PrOH = 90/10, detector: 215 nm, flow rate: 0.5 mL/min), t$_1$ = 19.2 min, t$_2$ = 31.9 min.
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