Chapter 2

Asymmetric Conjugate
Addition of Arylboronic Acids*

2.1 Introduction

Boronic acids are white crystalline solids, chemically stable at room temperature that can be stored for long time without any particular precaution. They present a low grade of toxicity, as evidenced by their use in medicine.\(^1\) Recently a boronic acid derivative (Velcade®) has been commercialized for antineoplastic therapy (Figure 2.1), as selective proteasome inhibitor and it finds application for treatment of refractory multiple myeloma.\(^2\)

\[ \text{Figure 2.1 The antineoplastic drug Velcade®.} \]

Boron has a vacant \( p \) orbital which confers mild Lewis acidity to boronic acids: the usual planar geometry of the boronic acid is modified by coordination of basic molecules to form stable tetrahedral adducts. With water the boronic acids can reversibly form tetrahedral boronates. (Scheme 2.1).

* Part of this chapter has been published, see: Gini, F.; Hessen, B.; Minnaard, A. J. Org. Lett. 2005, 7, 5309.
Boronic acids find a broad range of applications in synthetic chemistry. They are mostly used in cross coupling reactions to form biaryl units which are common in natural products, but also for other carbon-carbon forming processes, such as additions to \( \alpha,\beta \)-unsaturated compounds (vide infra) and 1,2-addition to carbonyl compounds, Heck coupling reactions, oxidative aminations and metal-catalyzed addition to imines. Furthermore they can be used as protecting groups for diols and diamines. Boronic acid derivatives are used as chiral Lewis acid in various processes. For instance chiral oxazaborolidines find broad applications in asymmetric reduction of prochiral ketones.

Arylboronic acids can be synthesized according to several procedures. The classical method describes the reaction of an aryl Grignard or aryl lithium reagent with a trialkylborate \( \text{B(OR)}_3 \), followed by hydrolysis of the resulting boronic ester. Recently Hartwig reported the one-pot synthesis of arylboronic acids by Ir-catalysed borylation of arenes (Scheme 2.2).³

**Scheme 2.1** Formation of tetrahedral boronates in \( \text{H}_2\text{O} \).

**Scheme 2.2** Ir-catalysed synthesis of arylboronic acids.
2.1.1 Cross-coupling reactions of organoboron compounds

In 1979, Suzuki and Miyaura discovered that alkenylboranes undergo palladium-catalysed coupling with various organic halides\(^4\) and subsequently in 1981 they described the palladium-catalysed coupling of arylboronic acids with aryl halides in the presence of a base.\(^5\) The latter reaction is known as the Suzuki-Miyaura coupling and has stimulated a great interest due to its versatility and the mild reaction conditions required.

The proposed catalytic cycle (Scheme 2.3) starts with the oxidative addition of the aryl or alkenyl halide or triflate to the Pd(0) complex with the formation of a Pd(II) species 2. The transmetalation with the arylboronic acid leads to the formation of Pd-aryl species 4 which undergoes reductive elimination to give the final product 5 and regenerating the active Pd(0) catalyst.

According to mechanistic studies, the presence of a base and water is necessary for the reaction to occur.\(^6\) The base leads, via the formation of OH\(^-\), to the generation of a boronate species [RB(OH)\(_3\)]\(^-\) which undergoes the transmetalation. Without the addition of a base, the energy barrier for the transmetalation process is too high.\(^6a\)
A recent publication of Whitehead and co-workers described the synthesis of boronate salts and their application in the Suzuki-Miyaura coupling reaction and in the Rh-catalyzed conjugate addition. In both cases the reaction proceeds smoothly and as clean as with phenylboronic acid and, obviously, in this case the Suzuki coupling does not require the addition of a base.

The coupling of organoboronic acids with alkenes in a Heck-type reaction has been recently investigated (see § 1.5.2). The reaction is known as “oxidative Heck reaction” and involves the use of a Pd(II) catalyst which transmetalates with the organoboron compound to form a Pd-aryl species. After the insertion in the olefinic double bond, the β-hydride elimination leads to the coupling product and to Pd(0) which is re-oxidated to Pd(II) by an additional oxidant.

2.1.2 Rh-catalysed conjugate addition of arylboronic acids

Miyaura, in 1997, reported the conjugate addition of organoboronic acids to enones catalyzed by a Rh(I)-dppb (1,4-bis-(diphenylphosphino)butane) complex. The optimization of the reaction conditions described in this first paper led to the publication of the asymmetric 1,4-addition of organoboron compounds in 1998 by Miyaura and Hayashi. Nowadays, this procedure is the method of choice for the asymmetric introduction of aryl groups. Excellent enantioselectivities have been reported for the addition to a large variety of α,β-unsaturated compounds. Next to BINAP, also phosphonites (A), amidophosphines (B), phosphoramidites (C) and chiral dienes (D) are used as chiral ligands (Figure 2.2).

The reactions are carried out in aqueous solutions, at temperatures up to 100 °C with a catalyst loading, in general, of 5.0 mol%. Nevertheless, the rhodium precursor, Rh(acac)(C\textsubscript{2}H\textsubscript{4})\textsubscript{2} is rather expensive and not easy to handle due to its air and moisture sensitivity. Therefore, there is a clear incentive to develop alternative catalysts able to afford comparable results.
2.2 Earlier work on Pd-catalysed conjugate additions.

The 1,4-addition to enones catalysed by Pd(II) complexes has been investigated with a variety of organometallic reagents, including organoboron compounds. Transmetalation from boron to palladium has been demonstrated in the cross-coupling of organoboron compounds with aryl and alkenyl halides and triflates (Suzuki coupling)\(^\text{15}\), as well as in the “oxidative Heck reaction” (see § 1.4.2), and cationic palladium(II) complexes show relatively fast rates for this process that is generally slow for transition metals.\(^\text{16}\)

The proposed general catalytic cycle for the conjugate addition of arylboronic acids is shown in Scheme 2.4.\(^\text{17}\) The cationic palladium species \(6\) transmetalates to the activated arylboronic acid,\(^\text{6}\) giving species \(7\). After coordination of the palladium complex to the carbon-carbon double bond of the enone, the aryl group is transferred to the \(\beta\) position forming an \(\alpha\)-palladate species \(10\). This is in equilibrium with the Pd-O enolate \(11\). Pd is known to be bounded mainly to the carbon atom\(^\text{18}\) in contrast to analogous Rh systems.\(^\text{19}\)

![Figure 2.2 Examples of chiral ligands used in Rh-catalysed conjugate addition of organoboronic acids: phosphonite (A), amidophosphine (B), phosphoramidites (C) and chiral diene (D).](image-url)
If the electronic properties of the enolate and its geometry allow the Pd and the hydrogen next to it to be in a syn orientation, β-hydride elimination can occur affording the Heck product, 12. Alternatively, the protonolysis of species 10 or 11 leads to the desired conjugate addition product, 13 and the initial cationic species 6. Cationic palladium enolates are much more susceptible to hydrolytic Pd-C bond cleavage than neutral palladium species and this is essential to avoid competing β-hydride elimination.18

Scheme 2.4 Proposed catalytic cycle for the Pd-catalysed conjugate addition of arylboronic acids and formation of Heck coupling product.

Palladium-catalysed 1,4-addition of arylboronic acids to enones was reported first by Uemura.20 The presence of a catalytic amount of SbCl3 resulted in the selective formation of conjugate addition product (Scheme 2.5). According to the authors, the coordination of the Lewis acid with the carbonyl group of the intermediate 15, to form 16, enhances the elimination of ClPdB(OH)2 leading to the formation of the antimony enolate 17. The subsequent protonation by AcOH affords the desired conjugate addition product 18. Without the addition of SbCl3, β-hydride elimination is favored and the main product observed is the corresponding
Heck coupling compound. Cyclic enones showed higher selectivity toward the conjugate addition product than acyclic enones. The addition of ArPdB(OH)$_2$ to the olefinic bond of the substrate occurs in syn fashion and therefore the direct syn-β hydride elimination in the resulting species 15 is precluded. On the other hand for acyclic enones the rotation along C$_α$-C$_β$ bond is possible and only the Heck coupling product is formed, although in low yield.

Scheme 2.5 Achiral 1,4-addition of arylboronic acids in presence of SbCl$_3$.

There is no strong evidence for a Pd(0) mediated catalytic process and the transmetalation of boronic species to Pd(II) can not be excluded, also taking in account that the reactions were not carried out under inert atmosphere and oxygen could oxidize the Pd(0) to Pd(II). Nevertheless, a study conducted by Moreno-Mañas, on Suzuki-type self-coupling of arylboronic acids demonstrated the possibility of Pd(0) catalysts to undergo oxidative addition of the C-B bond.$^{21}$

Miyaura et al. developed a Pd(II)-phosphine complex that by transmetalation with arylboronic acids performed conjugate addition more efficiently.$^{22}$ The reaction requires the presence of H$_2$O and proceeds smoothly in dioxane or THF, as the corresponding Rh-catalysed reaction. The presence of a base influenced the
outcome of the reaction resulting in the formation of the Heck-type compound, although as side product. Neutral palladium complexes such as [PdCl$_2$(dppe)] were not active and the catalyst of choice was [Pd(dppe)(PhCN)$_2$(SbF$_6$)$_2$] which was able to introduce both electron rich and electron poor arylboronic acids with good regioselectivity in cyclic and acyclic α,β-unsaturated systems, including enals (Scheme 2.6). However, the addition of boronic acids to α,β-unsaturated esters led to predominant formation of Heck coupling product.

![Scheme 2.6](image)

**Scheme 2.6** $Pd(II)/dppe$ catalysed conjugate addition of arylboronic acids and boroxine.

Lu et al. achieved conjugate addition of arylboronic acids using a palladium-bipyridine complex (Scheme 2.7). The reaction was performed at 40°C to decrease the protonolysis of arylboronic acids. From the screening of the reaction conditions it turned out that the use of 20 mol% of 2,2'-bipyridine was crucial to prevent formation of biphenyl, Heck-type product and the precipitation of Pd(0). Also the presence of H$_2$O was essential to improve the yield of the desired product. The catalyst was able to introduce different substituted aryl groups in the β position of a wide variety of enones, including α,β-unsaturated esters, which in previous examples showed preference for the formation of the Heck coupling product.

![Scheme 2.7](image)

**Scheme 2.7** $Pd(II)/bpy$ catalysed conjugate addition of arylboronic acids.
Recently, Lautens reported the addition of boronic acids to heterobicyclic alkenes achieving ring opening exclusively into the *cis* diastereoisomer using a Pd(DPPP)Cl₂ catalyst (Scheme 2.8).²⁴

**Scheme 2.8 Ring opening of heterobicyclic alkenes with arylboronic acids.**

Chiral Pd-complexes have been successfully used in the conjugate addition of aryltrifluoroborates (Scheme 2.9).¹⁷,²⁵ Cyclic enones afforded the product in higher enantioselectivities when the Pd(PhCN)₂(SbF₆)₂/(S,S)-Dipamp complex was used. For the reaction with acyclic substrates instead the complex formed with (S,S)-Chiraphos was more efficient. The reaction was carried out in aqueous MeOH and it required low temperatures. The addition of PhB(OH)₂ to 2-cyclohexenone at -5°C catalysed by the analogous achiral Pd(II)-dppe complex led to only 21% isolated yield.
Asymmetric Conjugate Addition of Arylboronic Acids

Scheme 2.9 *Asymmetric conjugate addition of aryltrifluoroborates.*

The asymmetric conjugate addition of arylboronic acids to activated ketones has been elusive until now, in spite of the readily availability of the reagents. The goal of our research was to develop an enantioselective version of the 1,4-addition of arylboronic acids to \( \alpha,\beta \)-unsaturated carbonyl compounds.
2.3 Palladium catalysed enantioselective conjugate addition of arylboronic acids

2.3.1 Development of the reaction

Initial experiments were carried out to explore the addition of phenylboronic acid 20a to 2-cyclohexenone 19a. In order to create an electrophilic Pd(II) complex with weakly coordinating anions, Pd(OAc)$_2$ was used in combination with triflic acid (TfOH) (Scheme 2.10).

![Scheme 2.10](image)

Of the bidentate ligands studied (Figure 2.3), the complexes based on Josiphos $L_1$ and its analogue $L_2$ did not show any activity over 48 h at 50°C. In contrast, the use of Me-DuPHOS $L_3$ gave full conversion to the desired product in 12 hours with an excellent 98% ee. The reaction afforded exclusively the desired conjugate addition product without traces either of the 1,2-addition product or the Heck coupling product. The same reaction carried out without the addition of triflic acid did not afford any conversion over 48 hours at 50°C.

Nevertheless, despite the consistently high ee, the rate of the reaction varied considerably from run to run. This inconsistency could be avoided by using Pd(O$_2$CCF$_3$)$_2$ instead of Pd(OAc)$_2$/TfOH, suggesting it had its origin in the acetate/triflate exchange reaction. This led to reproducible and shorter reaction times without affecting the ee (Table 2.1, entry 1). The catalyst loading could be decreased, and on a 1.0 mmol scale, 85% yield and 98% ee was obtained with 1.0 mol% of catalyst in 30 h (entry 2).
Asymmetric Conjugate Addition of Arylboronic Acids

Figure 2.3 Bidentate ligands studied in the conjugate addition of phenylboronic acid to 2-cyclohexenone.

With these reaction conditions established, the performance of the related ligands $L_4$ and $L_5$ was studied (Figure 2.3). The application of Me-BPE $L_4$ resulted in a much slower reaction; after 24 hours only 25% conversion was observed (98% ee). Et-DuPHOS $L_5$, on the other hand, showed the same activity and excellent selectivity as Me-DuPHOS $L_3$ (Table 2.1, entry 4).

Table 2.1a Screening of ligands in the Pd-catalysed addition of phenylboronic acid to 2-cyclohexenone.

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand</th>
<th>time (h)</th>
<th>yield (%)b of 21</th>
<th>ee %c</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$L_3$</td>
<td>6</td>
<td>80 (21a)</td>
<td>98 (R)</td>
</tr>
<tr>
<td>2d</td>
<td>$L_3$</td>
<td>30</td>
<td>85 (21a)</td>
<td>98 (R)</td>
</tr>
<tr>
<td>3</td>
<td>$L_4$</td>
<td>24</td>
<td>ndf</td>
<td>98 (R)</td>
</tr>
<tr>
<td>4</td>
<td>$L_5$</td>
<td>6</td>
<td>80 (21a)</td>
<td>98 (R)</td>
</tr>
</tbody>
</table>

aReactions were carried out in THF/H$_2$O (10/1) in the presence of 5.0 mol% of Pd(O$_2$CCF$_3$)$_2$ and 5.5 mol% of ligand at 50 °C unless stated otherwise. All reactions gave full conversion (TLC and NMR) unless stated otherwise. bIsolated yields after column chromatography cAbsolute configuration between brackets. dReaction performed with 1.0 mol% of catalyst. e25% conversion.
In contrast to the reaction catalysed by the Pd(II)/MeDuPHOS complex, the reaction in presence of Pd(O\textsubscript{2}CCF\textsubscript{3})\textsubscript{2} without a chiral bispaphosphine ligand, afforded full conversion of 2-cyclohexenone into a 1:1 mixture of phenol and cyclohexanone (Scheme 2.11).

![Scheme 2.11](image)

**Scheme 2.11 Reaction of 2-cyclohexenone catalysed by Pd(OOCOCF\textsubscript{3})\textsubscript{2}.**

Although all reactions were performed in a (10/1) mixture of THF/H\textsubscript{2}O, reactions can be performed as well in pure THF. The reaction rates were somewhat decreased but the ee’s were unaffected. Hayashi observed that the rhodium catalyzed conjugate addition of phenylboronic acid not always needed the addition of a protic source, like H\textsubscript{2}O or alcohol, whereas the same reaction with its corresponding ester, dimethoxyphenylborane, did not afford conversion in absence of H\textsubscript{2}O.\textsuperscript{10} This might depend on the formation of boroxine in the reaction with boronic acids, which releases the water necessary for the catalytic cycle.

### 2.3.2 Scope of the reaction: boronic acids

In the next stage, the scope of this new method for various boronic acids was examined, applying L\textsubscript{3} as the ligand and 19a as the substrate (Table 2.2). High yields and excellent ee’s were obtained in the addition of ortho-, meta-, and para- tolylboronic acid (Figure 2.4, Table 2.2). Also the electron rich ortho-, and meta-anisylboronic acids afforded the expected products in high yield and excellent ee. In contrast, meta-nitrophenylboronic acid did not react, whereas meta-chlorophenylboronic acid gave incomplete conversion (Table 2.2, entry 7). This parallels the observations by Larhed et al. in the corresponding oxidative Heck arylation. They observed that electron-rich arylboronic acids were the most reactive whereas the m-substituted electron-poor arylboronic acids afforded poor
yield and the $p$-substituted electron-poor arylboronic acids were completely unreactive. Larhed explained the lack of reactivity by a slow transmetalation of the arylboronic acids on the Pd(II) complexes.\textsuperscript{26}

![Substituted arylboronic acids.](image)

**Figure 2.4** Substituted arylboronic acids.

<table>
<thead>
<tr>
<th>entry</th>
<th>ArBX$_2$</th>
<th>time (h)</th>
<th>yield (%) of 21</th>
<th>ee %$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>20b</td>
<td>18</td>
<td>80 (21b)</td>
<td>99 (R)</td>
</tr>
<tr>
<td>2</td>
<td>20c</td>
<td>18</td>
<td>&gt;99 (21c)</td>
<td>99 (R)</td>
</tr>
<tr>
<td>3</td>
<td>20d</td>
<td>18</td>
<td>&gt;99 (21d)</td>
<td>97 (+)</td>
</tr>
<tr>
<td>4</td>
<td>20e</td>
<td>18</td>
<td>98 (21e)</td>
<td>98 (+)</td>
</tr>
<tr>
<td>5</td>
<td>20f</td>
<td>18</td>
<td>90 (21f)</td>
<td>97</td>
</tr>
<tr>
<td>6</td>
<td>20g</td>
<td>24</td>
<td>0 (21g)</td>
<td>-</td>
</tr>
<tr>
<td>7</td>
<td>20h</td>
<td>24</td>
<td>40 (21h)$^d$</td>
<td>98</td>
</tr>
<tr>
<td>8</td>
<td>20i</td>
<td>24</td>
<td>0</td>
<td>-</td>
</tr>
</tbody>
</table>

$^a$Reactions were carried out in THF/H$_2$O (10/1) in the presence of 5 mol% of Pd(O$_2$CCF$_3$)$_2$ and 5.5 mol% of (R,R)-Me-DuPHOS at 50 °C unless stated otherwise. All reactions gave full conversion (TLC and NMR) unless stated otherwise. $^b$Isolated yields after column chromatography $^c$Absolute configuration between brackets. $^d$Reaction performed with 1 mol% of catalyst. $^e$60% conversion.
The introduction of an alkenyl moiety is particularly interesting as it allows further functionalization of the molecule. Unfortunately using the optimized reaction conditions for the addition of aryl groups, vinylboronic acid \( 20i \) did not afford any conversion.

### 2.3.3 Scope of the reaction: substrates

To screen the scope of the reaction with respect to the substrate, different \( \alpha,\beta \)-unsaturated compounds were tested in the addition of phenylboronic acid catalysed by the \( \text{Pd(OCCF}_3\text{)}_2/\text{MeDUPHOS} \) complex (Figure 2.5).

![Figure 2.5 Structures of \( \alpha,\beta \)-unsaturated compounds.](image)

2-Cyclopentenone \( 19b \) afforded full conversion at 50°C in less than 4 h (Table 2.3, entry 1). The reaction was therefore carried out at room temperature and in 6 h the desired conjugate addition product was obtained in 75% yield and with 82% ee (entry 2). A comparable ee was obtained in the addition to 2-cycloheptenone (86% ee) leading to \( 21j \) (entry 3). The use of \((R,R)\)-EtDuPhos \( L_5 \) (Figure 2.1) both in the reaction with 2-cyclopentenone (entry 4) and 2-cycloheptenone (entry 5) led to virtually the same results.

Dihydropyridone \( 19e \) is an important substrate in the synthesis of alkaloids. It has proven to be a challenging substrate in the rhodium-catalyzed boronic acid
addition due to its low reactivity.\textsuperscript{13a,27} By applying the Pd(O\textsubscript{2}CCF\textsubscript{3})\textsubscript{2}/Me-DuPHOS catalyst at 70 °C, however, the reaction went to full completion and afforded the product with essentially complete enantioselectivity (>99% ee) (entry 6).

The formation of all-carbon quaternary centers by conjugate addition of organometallics reagents to β-substituted-α,β-unsaturated compounds still represents a challenge. The steric hindrance hampers a further substitution at the β position and especially the induction of enantioselectivity needs very efficient

Table 2.3 \textsuperscript{a} Screening of α,β-unsaturated compounds.

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate 19</th>
<th>ArBX\textsubscript{2} 20</th>
<th>time (h)</th>
<th>yield (%)\textsuperscript{b} of 21</th>
<th>ee %\textsuperscript{c}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>19b</td>
<td>20a</td>
<td>4</td>
<td>nd\textsuperscript{d}</td>
<td>80 (R)</td>
</tr>
<tr>
<td>2'</td>
<td>19b</td>
<td>20a</td>
<td>6</td>
<td>75 (21i)</td>
<td>82 (R)</td>
</tr>
<tr>
<td>3'</td>
<td>19c</td>
<td>20a</td>
<td>18</td>
<td>55 (21j)</td>
<td>86 (R)</td>
</tr>
<tr>
<td>4'</td>
<td>19b</td>
<td>20a</td>
<td>4</td>
<td>nd\textsuperscript{d}</td>
<td>83 (R)</td>
</tr>
<tr>
<td>5'</td>
<td>19c</td>
<td>20a</td>
<td>18</td>
<td>nd\textsuperscript{d}</td>
<td>85 (R)</td>
</tr>
<tr>
<td>6'</td>
<td>19e</td>
<td>20a</td>
<td>22</td>
<td>60 (21l)</td>
<td>&gt;99 (R)</td>
</tr>
<tr>
<td>7</td>
<td>19f</td>
<td>20a</td>
<td>24</td>
<td>0 (21m)</td>
<td>-</td>
</tr>
<tr>
<td>8</td>
<td>19g</td>
<td>20l\textsuperscript{a}</td>
<td>18</td>
<td>45 (21n)\textsuperscript{d}</td>
<td>82</td>
</tr>
<tr>
<td>9</td>
<td>19d</td>
<td>20l\textsuperscript{a}</td>
<td>5</td>
<td>75 (21k)</td>
<td>94 (S)</td>
</tr>
<tr>
<td>10</td>
<td>19h</td>
<td>20l\textsuperscript{a}</td>
<td>24</td>
<td>30 (21o)\textsuperscript{d}</td>
<td>49</td>
</tr>
<tr>
<td>11</td>
<td>19i</td>
<td>20a</td>
<td>22</td>
<td>nd (21p)\textsuperscript{d,e}</td>
<td>8\textsuperscript{m}</td>
</tr>
<tr>
<td>12</td>
<td>19j</td>
<td>20a</td>
<td>22</td>
<td>0 (21q)</td>
<td>-</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Reactions were carried out in THF/H\textsubscript{2}O (10/1) in the presence of 5 mol% of Pd(O\textsubscript{2}CCF\textsubscript{3})\textsubscript{2} and 5.5 mol% of (R,R)-Me-DuPHOS at 50 °C unless stated otherwise. All reactions gave full conversion (TLC and NMR) unless stated otherwise. \textsuperscript{b}Isolated yields after column chromatography. \textsuperscript{c}Absolute configuration between brackets. \textsuperscript{d}Not determined. \textsuperscript{e}Reaction performed at room temperature. \textsuperscript{f}19c was purchased with 80% purity. \textsuperscript{g}(R,R)-Et-DuPHOS was used as chiral ligand. \textsuperscript{h}A solution of 20 vol% of water in THF was added at 0.1 ml/h by means of a syringe pump during the reaction time (see Experimental part). \textsuperscript{i}Reaction performed at 70°C. \textsuperscript{j}60% conversion. \textsuperscript{k}42% conversion. \textsuperscript{l}The crude reaction mixture consisted of 27% of 21p, and 73% of Heck coupling product 24. \textsuperscript{m}ee of the 1,4-product.
catalysts. The addition of PhB(OH)$_2$ to 3-methyl-2-cyclohexenone 19f in the presence of 5.0 mol% Pd(OCOCF$_3$)$_2$/MeDUPHOS complex in a mixture of THF/H$_2$O (10/1) at 70°C gave no conversion and the starting material could be recovered (entry 7).

The water present in the mixture plays an important role in the catalytic cycle, protonating the $\alpha$-palladated intermediate (species 10 in Scheme 2.4), thus leading to the desired product, and regenerating the active catalyst. On the other hand water causes protodeboronation of phenylboronic acid forming benzene and B(OH)$_3$ (Scheme 2.4), especially when the reaction temperature is high. In order to achieve full conversion of the substrate, boronic acids are usually used in excess. Nevertheless, less reactive substrates led to incomplete conversion even when the reaction times were extended. The use of boroxine has shown to be useful in the Rh-catalysed addition of arylboronic acids to unreactive compounds such as 1-alkenylphosphonates and N-protected-2,3-dihydro-4-pyridones improving both conversions and enantioselectivities.

2,4,6-Triphenylboroxine is a cyclic trimeric anhydride derived from the dehydration of phenylboronic acid (Scheme 2.12). It can be synthesized smoothly by azeotropic removal of water from a xylene solution of phenylboronic acid or by heating neat boronic acid in vacuo at 145°C. In the presence of water, phenylboronic acid and boroxine are in equilibrium even at room temperature. By addition of H$_2$O each molecule of boroxine releases 3 molecules of phenylboronic acid.

![Scheme 2.12 Equilibrium between phenyl boronic acid and phenylboroxine.](image)

Phenylboroxine was used for the addition to linear substrates, that are known to be less reactive than the cyclic ones. However, 3-octen-2-one 19g showed only 60% conversion (45% yield) in 18 h (Table 2.1, entry 8). No Heck-type products were observed and a good 82% ee was obtained.

In order to study whether the substrate scope could be extended beyond enones, lactone 19d was subjected to the same reaction conditions. The reaction was fast affording full conversion in 5 hours with a high 94% ee (entry 9). It is interesting to
note that the conjugate addition product was obtained with the (S) absolute configuration, in contrast to the other cyclic substrates. The reason for this is not clear. Also this substrate did not give 1,2-addition or Heck-type products.

A challenging substrate to study was the unsaturated aldehyde 19h. The competitive formation of the 1,2-addition product often represents the major drawback of conjugate addition to this substrate and also the asymmetric rhodium-catalysed reaction has been troublesome. The group of Carreira reported excellent results in the conjugate addition to aryl-substituted enals. The sole paper on the use of aliphatic enals as substrates reported 56% yield and 92% ee in the conjugate addition of phenylboronic acid to 2-E-hexenal using [Rh(R-BINAP)(norbornadiene)]BF₄ as a catalyst. In the corresponding palladium-catalysed conjugate addition of boronic acids using an achiral ligand (dppe), good yields were obtained. Interestingly, using Pd(O₂CCF₃)₂/Me-DuPHOS as the catalyst, 2-E-hexenal underwent selective conjugate addition, without formation of the 1,2-addition product. The conversion was only 42%, however, and a moderate 49% ee was obtained (entry 10), which comes close to the results reported with triphenylbismuth.

In sharp contrast to the reaction of 19g and 19h, the addition to methyl-E-crotonate took a different course (Scheme 2.13). In this reaction the Heck coupling product dominates, together with 27% of racemic conjugate addition product. This parallels the results in the Pd(dppe)(PhCN)₂(SbF₆)₂ catalyzed addition of phenylboronic acid to ethyl acrylate.

The attempt to use methyl 2-acetamido acrylate 19j as substrate only resulted in recovery of starting material (entry 12).

Scheme 2.13 Reaction of methyl-E-crotonate with phenylboronic acid.
2.4 Reactions in iPrOH

The arylboronic acid needs to be activated by a nucleophile in order to undergo transmetalation to palladium. The formation of the active boronate intermediate, both in the rhodium-catalysed systems and in our optimized reaction conditions, relies on the presence of water in the mixture. Other solvents able to activate the boronic acid are alcohols.

The effect of MeOH and iPrOH was investigated in the benchmark reaction of 2-cyclohexenone with phenylboronic acid.

In a (10/1) mixture MeOH/H$_2$O at 60$^\circ$C the reaction went to full completion in 2 h, whereas in THF/H$_2$O (10/1) full conversion was achieved in 6 h, and the 1,4-addition product was obtained in 96% ee. However, besides the desired product, also 40% of the corresponding acetal was formed.

The same reaction in a (10/1) mixture iPrOH/H$_2$O at 70$^\circ$C did not lead to acetal formation, as expected. The conjugate addition product $21a$ was selectively formed in 3 h, with complete enantioselectivity in 80% yield (Scheme 2.14).

**Scheme 2.14 Conjugate addition of phenylboronic acid to 2-cyclohexenone in iPrOH/H$_2$O.**

In view of the fact that the alcohol can play the same role as H$_2$O, the reaction was carried out in pure iPrOH. The reaction time was much longer and full conversion was achieved in 22 h. A possible explanation is the formation of the boronic ester, PhB(OiPr)$_2$, which makes difficult the nucleophilic activation of the boron by iPrOH due to steric hindrance, leading to a much slower reaction. On the contrary, H$_2$O provides $\text{–OH}$ that can activate the organoboron reagent. However, also in this case the conjugate addition product was obtained with 99% ee although it was isolated in only 65%, while the rest of the crude mixture consisted of cyclohexanone as shown by GC analysis. The low rate of the conjugate addition allows the formation of a Pd-H species able to reduce the carbon-carbon double bond by transfer hydrogenation (see Chapter 4).
The linear substrates 19g and 19h in THF/H₂O showed poor reactivity affording only incomplete conversion. In the (10/1) mixture iPrOH/ H₂O, acyclic enone 3-octen-2-one afforded only 20% conversion in 24 h, while for 2-E-hexenal 19h the result was comparable to the reaction in THF/H₂O: 50% conversion in 24 h with 45% ee. Also for methyl-E-crotonate 19i the results of the reaction in iPrOH/ H₂O (10/1) did not improve: full conversion was achieved in 5 h resulting in a mixture of 86% of Heck coupling product and 24% of conjugate addition product.

2.5 Asymmetric addition of other arylboron reagents to 2-cyclohexenone

The excellent reactivity observed when using arylboronic acids prompted us to investigate the reactivity of different arylboron derivatives. Aryltrifluoroborates have been widely used as alternatives of arylboronic acids in cross coupling reactions and in Rh-catalysed conjugate additions. Miyaura et al. reported the asymmetric Pd(II)-catalysed 1,4-addition of aryltrifluoroborates to cyclic and acyclic enones with excellent enantioselectivities. Organotrifluoroborates present some advantages over boronic acids. As mentioned before, boronic acids often contain boroxine, which is much less reactive that the corresponding acid. Moreover their purification is not easy. Trifluoroborates are stable to air and moisture, can be stored at room temperature for a long time without decomposition and their synthesis is straightforward from the corresponding boronic acid. In Rh-catalyzed reactions it has been shown that aryltrifluoroborates usually react faster than the corresponding boronic acids and afford higher yields. This is ascribed to a faster transmetalation step of the tetracoordinated boron. The presence of water increases the reaction rate, probably because of the poor solubility of potassium salts in organic media. Molander and co-workers thoroughly investigated the use of organotrifluoroborates as alternative of boronic acids in the Suzuki cross-coupling. The exchange of one fluoride with an hydroxyl group generates an intermediate which undergoes transmetalation (Scheme 2.15).
When a catalyst formed from Pd(OCOCF$_3$)$_2$ and (R,R)-MeDUPHOS was used in the conjugate addition of PhB(OH)$_2$ to 2-cyclohexenone in a (10/1) mixture THF/H$_2$O at 50°C, full conversion was achieved in 6 h and 80% of 3-phenyl cyclohexanone was obtained with 98% ee (see § 2.3.1). Under the same reaction conditions, PhBF$_3$K (20k) fully converted the starting material into the desired product with almost complete enantioselectivity in 2.5 h (Scheme 2.16). A significant increase in reaction rate was therefore achieved.

Applying our standard reaction conditions, the reaction of 2-cyclohexenone with sodium trihydroxyphenylborate 20l reached full conversion in 22 h. Unfortunately,
besides the desired 1,4-addition product with only 60% ee, also a considerable amount of phenol and cyclohexanone were detected by GC analysis (Scheme 2.17).

Scheme 2.17 Conjugate addition of sodium trihydroxyphenylborate to 2-cyclohexenone.

On the contrary to the previous examples, the use of 20l leads to a basic medium. This makes the protonation of the α-palladate species 10 less probable, decreasing the overall reaction rate and enhancing the side products formation. Moreover Pd⁰ ("palladium black") was detected in the crude mixture. The same reaction carried out in absence of H₂O gave no conversion probably due to poor solubility of the borate salt in the organic media.

2.6 Conclusions

In conclusion, we have shown that the palladium-catalysed asymmetric conjugate addition of boronic acids is possible. Up to now this is the only palladium-based system able to catalyse the asymmetric conjugate addition of arylboronic acids to α,β-unsaturated enones. A catalyst based on palladium trifluoroacetate and Me-DuPHOS affords excellent results for several substrates, comparable to the best rhodium-based systems. The method is readily applicable: the catalyst is formed in situ at room temperature and both the ligand and Pd(O₂CCF₃)₂ are commercially available. Reaction conditions are mild and the scope seems to be broad, although further study is required to improve the performance with non-cyclic substrates.

For linear substrates results are unsatisfactory as yet and the reactivity did not improve even when the reactions were carried out in a mixture iPrOH/H₂O, where the rate of the reaction with 2-cyclohexenone was instead increased. The presence
of H$_2$O is still needed to avoid the formation of side products and to achieve a fast reaction.

The complete absence of Heck-type products, although in accordance with the literature, is nevertheless remarkable. α,β-Unsaturated enones and enals tend to form conjugate addition products and not the Heck coupling product. The different reactivity of esters and, moreover, the complete absence of enantioselectivity, in contrast with all the other substrates studied, is not understood yet.

A significant advantage over existing palladium-catalysed conjugate additions is the application of arylboronic acids instead of the less readily available aryltrifluoroborates and triarylbuminths. However, phenyl trifluoroborate showed the highest reactivity, in accordance with the Rh-catalysed systems. Sodium trihydroxyphenylborate instead showed poor reactivity, both in terms of chemoselectivity and enantioselectivity. The formation of phenol and cyclohexanone can be ascribed to the slow reaction rate, thus allowing the side reaction to occur. This is in contrast with the literature evidence of a comparable reactivity of the borate salts compared to the arylboronic acids.

## 2.7 Experimental section

**General experimental**

$^1$H NMR spectra were recorded at 300 or 400 MHz with CDCl$_3$ as solvent. $^{13}$C NMR spectra were obtained at 75.4 or 100.6 MHz in CDCl$_3$, (Varian VXR300 or AMX400 spectrometers). Chemical shifts were determined relative to the residual solvent peaks ($\delta = 7.26$ ppm for hydrogen, $\delta = 77.0$ for carbon). Data are reported as follows: chemical shifts, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet) and coupling constants (Hz). Mass spectra were recorded on a AEI-MS-902 mass spectrometer. Enantioselectivities were determined by capillary GC analysis (ChiralDEX G-TA column (30 m x 0.25 mm) or ChiralDEX α-TA column (30 m x 0.25 mm)) using a flame ionization detector and compared with the racemic 1,4 addition products. HPLC analysis was carried out on a Shimadzu LC-10ADVP HPLC equipped with a Shimadzu SPD-M10A VP diode array detector. Conversion of the reaction was determined by GC-MS (GC, HP6890: MS HP5973) with an HP1 or HP5 column (Agilent
Asymmetric Conjugate Addition of Arylboronic Acids

Technologies, Palo Alto, CA). Thin-layer chromatography (TLC) was performed on silica gel, components were visualized by staining with KMnO₄ reagent. Flash chromatography was performed on silica gel. All reactions were carried out under nitrogen atmosphere using dried glassware. All solvents were dried and distilled before use according to standard procedures.

Ligand L₁ was provided by Solvias, L₂ was purchased from Fluka and L₃, L₄, L₅ were purchased from Strem. All starting materials and products have been described in the literature.

Racemic 21k was prepared by reaction of 19d with phenylmagnesium bromide in dry THF at 0 °C in the presence of CuCl (3 mol%) and TMSCl (1.1 eq.). Both enantiomers of 21l were synthesized by the asymmetric rhodium/phosphoramidite catalyzed addition of phenylboronic acid to 19e according to the reported procedure.¹³a

Racemic 21n was prepared by reaction of trans-4-phenyl-3-buten-2-one with n-butylmagnesium bromide in dry Et₂O at 0°C in the presence of stoichiometric CuI.

The Heck coupling product 24 was synthesized by reaction of 19i with iodobenzene in NMP in the presence of Pd(OAc)₂ (0.05 mol%).⁴¹

**Synthesis of racemic 3-Phenylhexanal (21o)⁴²**

A solution of Et₃N (5 mmol, 0.7 mL) in hexane (2.5 mL) was added dropwise to a solution of cinnamoyl chloride (4.5 mmol, 750 mg) and EtSH (4.5 mmol, 0.34 mL) in hexane (10 mL) at 0°C. The mixture was allowed to reach room temperature and stirred overnight. The precipitate was filtered off and washed with hexane/Et₂O (1:1). Purification of the crude by column chromatography (pentane/ Et₂O = 50:1) afforded the (E)-3-phenyl-thioprop-2-ene-oic acid (S)-ethyl ester as colorless oil (563 mg, 2.9 mmol, 65%). The ethyl ester was dissolved in dry Et₂O (20 mL) in the presence of CuI (100 mol%, 2.9 mmol, 552 mg) and n-PrMgBr (3.09 M in Et₂O, 1.2 eq., 3.5 mmol, 1.2 mL) was added dropwise at 0°C. After stirring for 30 min at rt, sat. aqueous NH₄Cl was added dropwise, the organic layer was concentrated and the crude product was purified by column chromatography (pentane/ Et₂O = 50:1) to yield the 1,4-addition product 3-phenyl-thiohexanoic acid (S)-ethyl ester (130 mg, 0.6 mmol, 20%). The product was dissolved in CH₂Cl₂ (1 mL) and 10% Pd/C
(5 mol%, 30 mg) was added at rt under nitrogen. After addition of Et₃SiH (3 eq., 1.8 mmol, 0.3 mL) the mixture was stirred at rt overnight and then filtered over Celite washing with CH₂Cl₂. Purification by column chromatography (pentane/Et₂O =100:1) afforded racemic 3-phenylhexanal 21o as colorless oil (40 mg, 0.23 mmol, 41 %).

**General procedure for the palladium catalyzed asymmetric conjugate addition of arylboronic acids**

In a flame dried Schlenk tube equipped with septum and stirring bar, Pd(OCOCF₃)₂ (5.0 mol%, 5.0 µmol, 1.66 mg) and ligand L₃ (5.5 mol%, 5.5 µmol, 1.68 mg) were dissolved in dry THF (1.0 mL) and stirred under nitrogen at room temperature for 10 min. Arylboronic acid 20 (3.0 eq., 0.30 mmol) was added, followed by the addition of enone 19 (0.1 mmol). After the addition of H₂O (0.1 mL), the mixture was degassed by alternating vacuum-nitrogen cycles and then heated to 50°C. When the reaction was complete according to TLC analysis, the mixture was cooled down to room temperature and sat. aqueous NaHCO₃ solution was added. The organic phase was separated and the resulting aqueous layer was extracted with Et₂O. The combined organic phases were filtered over a plug of silica, dried on MgSO₄, concentrated and the residue purified by flash chromatography (Et₂O/pentane) to yield the corresponding products 21. The composition and the conversion in the crude mixture were determined by NMR and GC-MS analysis.

(R)-3-Phenyl-cyclohexanone (21a)³³

Ketone 21a was obtained after purification by flash chromatography (eluent pentane/Et₂O 5:1) in 80% yield, 98% ee. ¹H-NMR δ 1.69-1.86 (2H, m), 2.02-2.14 (2H, m), 2.29-2.58 (4 H, m), 2.93-2.99 (1H, m), 7.17- 7.31 (5H, m); ¹³C-NMR δ 211.5, 144.3, 128.7, 126.7, 126.6, 48.9, 44.7, 41.2, 32.8, 25.5. MS, m/z (%): 174 (M+, 100), 131 (68.4), 117 (86.8). HRMS for C₁₂H₁₄O calcd 174.1045, found 174.1055. E.e. was determined by HPLC analysis, Chiralpak AD column, Heptane/i-PrOH 99:1, detection at 209 nm, retention times: 12.1 (S) / 13.8 (R) min.
Asymmetric Conjugate Addition of Arylboronic Acids

(+)-(R)-3-(2-Methoxyphenyl)-cyclohexanone (21b)

Ketone 21b was obtained after purification by flash chromatography (elucent pentane/Et₂O 5:1) in 80% yield, 99% ee. 

\[ \begin{align*} 
{^{1}H-NMR} & \delta 1.75-2.14 (4H, m), 2.32-2.60 (4H, m), 3.37-3.48 (1H, m), 3.81 (3H, s), 6.85-6.95 (2H, m), 7.16-7.26 (2H, m). 
MS, m/z (\%): 204 (M+, 91.9), 147 (100), 91. 
HRMS for C₁₃H₁₆O₂ calcld 204.1150, found 204.1161. 
E.e. was determined by chiral HPLC analysis, Chiralcel OD column, Heptane/i-PrOH 95:5, detection at 210 nm, retention times: 8.1 (S) / 9.0 (R) min. 
\end{align*} \]

(+)-(R)-3-(2-Methylphenyl)-cyclohexanone (21c)

Ketone 21c was obtained from the reaction of 19a with 20c in quantitative yield without further purification in 99% ee. 

\[ \begin{align*} 
{^{1}H-NMR} & \delta 1.75-1.82 (2H, m), 1.94-1.98 (1H, m), 2.11-2.15 (1H, m), 2.28 (3H, s), 2.35-2.48 (4H, m), 3.11-3.22 (1H, m), 7.11-7.21 (4H, m). 
MS, m/z (\%): 188 (M+, 100), 145 (92.4), 131 (81.3). 
HRMS for C₁₃H₁₆O calcld 188.1201, found 188.1212. 
E.e. was determined by chiral HPLC analysis, Chiralpak AD column, Heptane/i-PrOH 99:1, detection at 209 nm, retention times: 9.3 (S) / 11.63 (R) min. 
\end{align*} \]

(+)-3-(3-Methylphenyl)-cyclohexanone (21d)

Ketone 21d was obtained from the reaction of 19a with 20d in quantitative yield without further purification in 97% ee. 

\[ \begin{align*} 
{^{1}H-NMR} & \delta 1.68-1.83 (2H, m), 2.01-2.13 (2H, m), 2.30 (3H, s), 2.34-2.53 (4H, m), 2.89-2.92 (1H, m), 6.96-7.02 (3H, m), 7.15-7.21 (1H, m). 
MS, m/z (\%): 188(M+, 100), 145 (52.6), 131 (85). 
HRMS for C₁₃H₁₆O calcld 188.1201, found 188.1210. 
E.e. was determined by chiral HPLC analysis, Chiralpak OD column, Heptane/i-PrOH 99:1 grad. 90/10, detection at 209 nm, retention times: 11.37 (Min) / 13.61 (Maj) min. 
\end{align*} \]
(+) -3-(3-Methoxyphenyl)-cyclohexanone (21e)\textsuperscript{43}

Ketone 21e was obtained after purification by flash chromatography (eluuent pentane/Et\textsubscript{2}O 5:1) in 98\% yield, 98\% ee. \textsuperscript{1}H-NMR $\delta$ 1.65-1.82 (2H, m), 2.01-2.13 (2H, m), 2.29-2.58 (4H, m), 2.89-2.97 (1H, m), 3.75 (3H, s), 6.71-6.78 (3H, m), 7.17-7.23 (1H, m). MS, $m/z$ (%): 204 (M+, 100), 163 (29.3), 134 (51.0). HRMS for C\textsubscript{13}H\textsubscript{16}O\textsubscript{2} calcd 204.115, found 204.116. E.e. was determined by chiral HPLC analysis, Chiralcel OD column, Heptane/i-PrOH 99:1, detection at 210 nm, retention times: 33.7 (Min) / 38.3 (Maj) min.

(+) -3-p-Tolyl-cyclohexanone (21f)\textsuperscript{42}

Ketone 21f was obtained after purification by flash chromatography (eluuent pentane/Et\textsubscript{2}O 5:1) in 90\% yield, 97\% ee. \textsuperscript{1}H-NMR $\delta$ 1.70-1.81 (2H, m), 2.00-2.13 (2H, m), 2.29 (3H, s), 2.30-2.55 (4H, m), 2.89-2.96 (1H, m), 7.06-7.22 (4H, m). \textsuperscript{13}C-NMR $\delta$ 211.05, 141.4, 136.2, 129.3, 126.4, 49.1, 44.4, 41.2, 32.9, 25.6, 20.96. MS, $m/z$ (%): 188 (M+, 51.9), 145 (25.5), 131 (100). HRMS for C\textsubscript{13}H\textsubscript{16}O calcd 188.1201, found 188.1215. E.e. was determined by chiral HPLC analysis, Chiralpak AD column, Heptane/i-PrOH 98:2, detection at 209 nm, retention times: 7.3 (Min) / 7.65 (Maj) min or by chiral GC, Chiraldex G-TA column (30 m x 0.25 mm) 140 °C, retention times: 52.9 (Maj) / 54.6 (Min) min.

3-(3-Chlorophenyl)-cyclohexanone (21h)\textsuperscript{33}

2-Cyclohexenone gave 60\% of conversion in 21h that was obtained after purification by flash chromatography (eluuent pentane/Et\textsubscript{2}O 5:1) in 40\% yield, 98\% ee. \textsuperscript{1}H-NMR $\delta$ 1.66-1.96 (2H, m), 2.02-2.12 (2H, m), 2.27-2.56 (4H, m), 2.88-2.96 (1H, m), 7.01-7.14 (1H, m), 7.15-7.22 (3H, m); \textsuperscript{13}C-NMR $\delta$ 210.4, 146.3, 134.5, 129.9, 126.9, 126.8, 124.8, 48.6, 44.4, 41.1, 32.5, 25.4. E.e. was determined by chiral HPLC analysis, Chiralcel AD column, Heptane/i-PrOH 98:2, detection at 254 nm, retention times: 8.8 (Min) / 9.9 (Maj) min.
(+)-(R)-3-Phenyl-cyclopentanone (21i)\(^{42}\)

Ketone 21i was obtained following the general procedure at room temperature after purification by flash chromatography (eluient pentane/Et\(_2\)O 5:1) in 75% yield, 82% ee. \(^1\)H-NMR \(\delta\) 1.89-1.97 (1H, m), 2.21-2.46 (4H, m), 2.63 (1H, dd, \(J = 6.96\) and 17.96 Hz), 3.34-3.41 (1H, m), 7.19-7.32 (5H, m); \(^{13}\)C-NMR \(\delta\) 218.5, 142.9, 128.6, 126.7, 45.7, 42.5, 38.8, 31.1. MS, \(m/z\) (%): 160 (M+, 82.8), 117 (37.6), 104 (100). HRMS for C\(_{11}\)H\(_{12}\)O calcd 160.0888, found 160.0896. E.e. was determined by chiral GC, Chiraldex \(\alpha\)-TA column (30 m x 0.25 mm) 140°C, retention times: 16.8 (S) / 18.6 (R) min.

\[ (+)-(R)-3-Phenyl-cycloheptanone (21j) \]

Ketone 21j was obtained after purification by flash chromatography (eluient pentane/Et\(_2\)O 5:1) in 53% yield, 86% ee. \(^1\)H-NMR \(\delta\) 1.43-1.47 (1H, m), 1.63-1.72 (2H, m), 1.93-2.06 (3H, m), 2.53-2.62 (3H, m), 2.85-2.92 (2H, m), 7.12-7.27 (5H, m); \(^{13}\)C-NMR \(\delta\) 213.3, 146.9, 128.6, 126.4, 51.2, 43.9, 42.7, 39.2, 29.7, 24.2. MS, \(m/z\) (%): 188 (M+, 100), 130 (57.4), 104 (82.8). HRMS for C\(_{13}\)H\(_{16}\)O calcd 188.1201, found 188.1208. E.e. was determined by chiral HPLC analysis, Chiralcel OD column, Heptane/i-ProOH 95:5, detection at 210 nm, retention times: 6.7 (S) / 7.2 (R) min.

\[ (+)-(R)-N-Carbobenzyloxy-2-Phenyl-4-piperidone (21l) \]

Piperidone 21l was obtained according to the general procedure, performing the reaction at 70°C, after purification by flash chromatography (eluient pentane/Et\(_2\)O 1:1) in 60% yield, >99% ee. \(^1\)H-NMR \(\delta\) 2.28-2.34 (1H, d, \(J = 16.11\) Hz), 2.42-2.79 (1H, m), 2.80-2.84 (1H, d, \(J = 3.66\) and 6.59 Hz), 2.93 (1H, d, \(J = 15.38\) Hz), 3.13 (1H, t, \(J = 11.35\) Hz), 4.21 (1H, bs), 5.11-5.21 (2H, m), 5.78 (1H, bs), 7.19-7.33 (10H, m); \(^{13}\)C-NMR \(\delta\) 207.2, 155.3, 139.6, 136.2, 128.8, 128.5, 128.2, 127.9, 126.7, 67.8, 54.6, 44.1, 40.5, 38.9. MS, \(m/z\) (%): 309 (M+), 218 (43), 132, 91 (100). E.e. was determined by chiral HPLC analysis, Chiralcel OD-H column, Heptane/i-ProOH 90:10, detection at 210 nm, retention times: 26.6 (S, not visible) / 31.6 (R) min.
CHAPTER 2

General procedure for the asymmetric conjugate addition of phenylboroxine

In a flame dried Schlenk tube equipped with septum and stirring bar, Pd(OOC(O)CF<sub>3</sub>)<sub>2</sub> (5.0 mol%, 5.0 µmol, 1.66 mg) and ligand L<sub>3</sub> (5.5 mol%, 5.5 µmol, 1.68 mg) were dissolved in dry THF (1.0 mL) and stirred under nitrogen at room temperature for 10 min. Phenylboroxine 20i (3.0 eq., 0.30 mmol, 94 mg) was added, followed by the addition of enone 1 (0.1 mmol). The resulting mixture was heated to 50°C and 0.4 mL of a 20 vol% solution of water in THF was added slowly by syringe pump (0.1 mL/h). After the addition, stirring was continued overnight and then the reaction mixture was cooled down to room temperature, diluted with Et<sub>2</sub>O and filtered over a plug of silica. The crude was dried, concentrated and purified by flash chromatography (Et<sub>2</sub>O/pentane) to yield the corresponding products 21. The composition and the conversion in the crude mixture were determined by NMR and GC-MS analysis.

(+)-(S)-4-Phenyl-tetrahydro-2H-pyran-2-one (21k)<sup>46</sup>

Pyranone 21k was obtained after purification by flash chromatography (eluent pentane/Et<sub>2</sub>O 3:2) in 75% yield, 94% ee.

^1H-NMR δ 1.97-2.02 (1H, m), 2.11-2.15 (1H, m), 2.59 (1H, dd, J = 10.6 and 17.6 Hz), 2.88 (1H, ddd, J = 1.8, 5.9 and 17.6 Hz), 3.18-3.21 (1H, m), 4.32-4.38 (1H, m), 4.43-4.48 (1H, m), 7.16-7.34 (5H, m). MS, m/z (%): 176 (M+, 100), 117 (85.8), 104 (82.4). HRMS for C<sub>11</sub>H<sub>12</sub>O<sub>2</sub> calcd 176.0837, found 176.0855. E.e. was determined by chiral GC, Chiraldex G-TA column (30 m x 0.25 mm), 170 °C, retention times: 123.0 (R) / 124.1 (S) min.

4-Phenyl-2-octanone (21n)<sup>47</sup>

3-Octen-2-one 19g gave 60% conversion to ketone 21n that was obtained after purification by flash chromatography (eluent pentane/Et<sub>2</sub>O 100:1) in 45 % yield and 82% ee.

^1H-NMR δ 0.78 (3H, t, J = 7.3), 1.04-1.26 (4H, m), 1.50-1.59 (2H, m), 1.96 (3H, s), 2.62-2.68 (2H, m), 3.03-3.08 (1H, m), 7.07-7.26 (5H, m); ^13C-NMR δ 207.9, 144.5, 128.4, 127.4, 126.2, 50.9, 41.2, 36.1, 30.6, 29.5, 22.5, 13.9. MS, m/z (%): 204 (M+, 17.2), 147 (80.2), 91 (100). HRMS for C<sub>14</sub>H<sub>20</sub>O calcd 204.1514, found 204.1524. E.e. was determined by chiral HPLC analysis, Chiralcel OB-H column,
Heptane/i-PrOH 99:1, detection at 210 nm, retention times: 13.6 (Maj) / 19.3 (Min) min.

3-Phenyl-hexanal (21o)

*Trans*-2-hexenal gave 42% conversion in aldehyde 21o that was obtained after purification by flash chromatography (eluent pentane/ Et₂O 100:1) in 30% yield and 50% ee. ¹H-NMR δ 0.82 (3H, t, J = 7.3 Hz), 1.11-1.18 (2H, m), 1.55-1.61 (2H, m), 2.67 (2H, dd, J = 1.83 and 6.97 Hz), 3.12-3.16 (1H, m), 7.13-7.28 (5H, m), 9.62 (1H, t, J = 2.2 Hz); ¹³C-NMR δ 202.1, 143.9, 128.6, 127.4, 126.5, 50.5, 39.8, 38.8, 20.4, 13.9. MS, m/z (%): 176 (M+, 8.1), 132 (57.9), 107 (79.9), 91 (100). HRMS for C₁₂H₁₆O calcd 176.1201, found 176.1237. E.e. was determined by chiral HPLC analysis, Chiralcel OD-H column, Heptane/i-PrOH 98:2, detection at 210 nm, retention times: 20.9 (Min) / 31 (Maj) min.

Procedure for the asymmetric conjugate addition of potassium phenyltrifluoroborate to 2-cyclohexenone

In a flame dried Schlenk tube equipped with septum and stirring bar, Pd(OCOCF₃)₂ (5.0 mol%, 25 µmol, 8.3 mg) and ligand L₃ (5.5 mol%, 27.5 µmol, 8.4 mg) were dissolved in dry THF (5.0 mL) and stirred under nitrogen at room temperature for 10 min. Potassium phenyltrifluoroborate 20j (2 eq., 1.0 mmol, 184 mg) was added, followed by the addition of 2-cyclohexenone 19a (0.5 mmol, 48.5 µL). After the addition of H₂O (0.5 mL), the mixture was degassed by alternating vacuum-nitrogen cycles and then heated to 50°C. The reaction was complete according to GC analysis after 2.5h. The mixture was cooled down to room temperature and aqueous NaHCO₃ sat. solution was added. The organic phase was separated and the resulting aqueous layer was extracted with Et₂O. The combined organic phases were filtered over a plug of silica, dried on MgSO₄, concentrated and purified by flash chromatography (Et₂O/pentane = 6/1) to yield the corresponding products 21a in 80% yield and 99% ee.
PROCEDURE FOR THE ASYMMETRIC CONJUGATE ADDITION OF SODIUM PHENYLBORATE TO 2-CYCLOHEXENONE

In a flame-dried Schlenk tube equipped with septum and stirring bar, Pd(OCOCF₃)₂ (5.0 mol%, 5.0 µmol, 1.66 mg) and ligand L₃ (5.5 mol%, 5.5 µmol, 1.68 mg) were dissolved in dry THF (1.0 mL) and stirred under nitrogen at room temperature for 10 min. Sodium phenylborate 20k (3.0 eq., 0.3 mmol, 48.3 mg) was added, followed by the addition of 2-cyclohexenone 19a (0.1 mmol, 9.7 µL) and n-dodecane (10 µL) as internal standard. The sample t₀ was taken and filtered over a small plug of silica. After the addition of H₂O (0.1 mL), the mixture was degassed by alternating vacuum-nitrogen cycles and then heated to 50°C. The reaction was complete after 22 h according to GC analysis and a black precipitate (Pd⁰) was present in the mixture. The composition of the crude as determined by GC analysis was: 15% 21a, 55% 22, 30% 23.

The solution was cooled down to room temperature and sat. aqueous NaHCO₃ solution was added. The organic phase was separated and the resulting aqueous layer was extracted with Et₂O. The combined organic phases were filtered over a plug of silica, dried on MgSO₄, concentrated and the residue purified by flash chromatography (Et₂O/pentane = 9/1) to yield the corresponding products 21a with 60% ee, as a mixture with phenol 23 (25%).

2.8 REFERENCES

The formation of trihydroxyboronates in solution is commonly accepted but in only few examples they have been isolated: (c) Fields, C. L.; Doyle, J. R. Thermochim. Acta 1974, 8, 239.
18 Albéniz, A. C.; Catalina, N. M.; Espinet, P.; Redón, R. Organometallics 1999, 18, 5571.


For a review, see: Lappert, M. F. Chem. Rev. 1956, 56, 959.

Comparable results were obtained by Miyaura et al. in the palladium/ChiraPHOS/Cu(BF4)2 catalyzed asymmetric addition of arylbismuth compounds leading to ee’s up to 85% for linear enones, see: Nishikata, T.; Yamamoto, Y.; Miyaura, N. Chem. Commun. 2004, 1822.


The palladium/ChiraPHOS/Cu(BF4)2 catalyzed addition of triphenylbismuth to 2-hexenal afforded the conjugate addition product in 55% yield, 68% ee, see: ref 31.


Substrate 14j has been used successfully in the corresponding rhodium-catalyzed reaction, see: Navarre, L.; Darses, S.; Genet, J.-P. Angew. Chem., Int. Ed. 2004, 43, 719 and references cited therein.

Asymmetric Conjugate Addition of Arylboronic Acids


44 For the absolute configuration determination of 21b, see: (a) ref. 43b. For the absolute configuration determination of 21c, see: (b) Hayashi, T.; Tokunaga, N.; Yoshida, K.; Han, J. W. J. Am. Chem. Soc. 2002, 124, 12102.

