Rhodium-catalyzed boronic acid additions
Jagt, Roelof Bauke Christiaan

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2006

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.
Chapter 4
Enantioselective Synthesis of Diarylmethanols

A ligand library approach revealed a bidentate phosphoramidite as an effective chiral ligand in the rhodium(I)-catalyzed addition of arylboronic acids to aldehydes providing up to 75% enantioselectivity and up to 96% isolated yield.¹

Chapter 4

4.1 Introduction

Enantiopure diarylmethanols are key building blocks for a number of biologically active compounds and are therefore important synthetic targets. The diarylmethane moiety is essential for the physiological activity of many organic compounds displaying antihistaminic, antiarrhythmic, diuretic, antidepressive, anticholinergic, local-anesthetic, and laxative activities, e.g. (+)-(R,R)-clemastine (1), (+)-(R)-neobenodine (2), and (+)-(S)-chlorpheniramine (3). Two different approaches for the synthesis of enantiopure diarylmethanols have been used (Scheme 4.1): a) asymmetric reduction of the corresponding prochiral diaryl ketones and b) the asymmetric addition of aryl organometallic reagents to aldehydes.

![Diagram of chiral pharmacophores with a diarylmethane moiety]

Figure 4.1 Chiral pharmacophores with a diarylmethane moiety

Scheme 4.1 Two different approaches for the synthesis of enantiopure diarylmethanols

Reduction methodologies are often highly efficient and cost-effective. In the current reaction, however, it requires a considerable electronical and/or stereochemical difference between the two aryl moieties in order to reach high enantioselectivity. Although high
Enantioselective Synthesis of Diarylmethanols

Enantioselectivities have been achieved with ortho-substituted benzophenones, simple meta- and para-substituted benzophenones were only hydrogenated with low or moderate enantioselectivities. The second method, the asymmetric addition of aryl organometallic reagents to aldehydes, seems more suitable for asymmetric induction because of the large steric and electronic differences between the aryl group and the hydrogen atom on an aldehyde substrate. Diphenylzinc has been used as a phenyl transfer reagent, but its background reaction with aldehydes makes it difficult to achieve high stereoselectivity. This undesired activity could be moderated by the simultaneous use of diethylzinc. Recently, Bolm et al. achieved excellent enantioselectivities employing a method in which the aryl transfer reagent was generated by mixing arylboronic acids with an excess of diethylzinc. Arylboronic acids have received increasing attention as arylating reagents because they are shelf stable, readily available, and compatible with a large variety of functional groups. From a practical point of view, the development of an efficient protocol for their direct addition to aldehydes would be highly desirable. The addition of arylboronic acids to aromatic aldehydes was initially reported by Miyaura in 1998 employing rhodium-catalysts. With MeO-MOP as chiral ligand, 41% ee was obtained for the addition of phenylboronic acid to 1-naphthaldehyde (Scheme 4.2). Subsequent attempts to improve the enantioselectivity of this reaction remained unsuccessful.

Scheme 4.2 The system of Miyaura et al.

Phosphoramidites are readily available ligands for asymmetric catalysis that have been applied in a host of transformations. Their modular build-up makes them easily tunable and therefore highly suitable for the synthesis of a diverse ligand library. Previous approaches to the optimization of phosphoramidite catalysts in our group involved the
preparative synthesis and purification of a range of different phosphoramidites.\textsuperscript{22} Recently, Lefort \textit{et al.} reported the automated solution-phase synthesis of 32 different phosphoramidite ligands and their \textit{in situ} screening in the rhodium-catalyzed hydrogenation.\textsuperscript{20a} In a collaboration with our group this technology was used to prepare and screen a library of 96 different phosphoramidites in the rhodium-catalyzed conjugate addition of vinyltrifluoroborates to cyclic and acyclic enones.\textsuperscript{20b} The automated parallel synthesis of ligands dramatically decreases the time period needed for catalyst optimization. Moreover, ligands can be prepared in relatively small quantities at the time they are required. This is particularly important for less stable ligands, but also makes the screening process more cost-effective. In this chapter the results are described of a similar ligand library approach in the search for a more selective catalyst for the arylboronic acid addition to benzaldehydes.

\section*{4.2 Results and Discussion}

\subsection*{4.2.1 Preliminary Studies and Mechanistic Considerations}

Preliminary studies were carried out with $p$-chlorobenzaldehyde (4a) as a substrate and 3 equiv of phenylboronic acid. Three catalyst systems that were previously reported to be successful in the related conjugate addition of arylboronic acids to enones were tested in the phenylboronic acid addition to 4a. The recently reported palladium/Me-DuPHOS system\textsuperscript{23} did not facilitate the reaction (Scheme 4.3, reaction a). The rhodium/BINAP catalyst,\textsuperscript{24} developed by Hayashi \textit{et al.}, gave the corresponding diarylmethanol 5a with 19\% enantioselectivity (reaction b). However, the conversion did not exceed 62\%, even after prolonged reaction times. To our delight, the rhodium/phosphoramidite-catalyst – developed in our group by Jean-Guy Boiteau\textsuperscript{25} – gave a promising 41\% ee (reaction c). Also here the conversion was not complete. With a catalyst prepared \textit{in situ} from 3 mol\% Rh(acac)(C\textsubscript{2}H\textsubscript{4})\textsubscript{2} and 7.5 mol\% phosphoramidite (S)-L\textsubscript{1}, after 4 h under the aqueous conditions that are commonly used for the conjugate addition reaction (1,4-dioxane/H\textsubscript{2}O: 10/1), the conversion was 79\%. Longer reaction times did not improve these results.
Enantioselective Synthesis of Diarylmethanols

**Scheme 4.3** Catalytic 1,2-addition of phenylboronic acid using three catalyst systems previously reported to be successful in their related conjugate addition to enones

In order to determine the effect of the solvent upon the conversion and enantioselectivity, different solvents were examined with and without water as a co-solvent (see Table 4.1). 2-Propanol (entry 5) appears to be the most suitable solvent for this reaction, increasing both reactivity and enantioselectivity. Full conversion was obtained within 4 h resulting in 52% ee. Interestingly, the reaction also proceeded in non-protic media without water as an additive (entries 7-14). In conjugate addition processes of arylboronic acids, water or alcohol additives have been proven essential to achieve catalytic activity (see Chapter 1, §1.3). If work-up with 12.5% aqueous ammonia was omitted in the current reaction, a mixture of product 5a and a considerable amount of a product related compound was found. This intermediate was identified as borate ester 6 (Scheme 4.4). We propose the mechanism can take two pathways, dependent on the availability of a proton source. Arylrhodium complex B is formed after transmetalation of the aryl group from boron to rhodium. After coordination of the substrate (complex C), insertion of 4 into the arylrhodium bond gives species D.

67
**Table 4.1 Solvent variation in the rhodium-catalyzed asymmetric addition of arylboronic acids to aldehydes**

![Chemical structure](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>conversion (%)</th>
<th>ee (%)&lt;sup&gt;cd&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1,4-dioxane/H₂O: 10/1</td>
<td>79</td>
<td>41 (S)</td>
</tr>
<tr>
<td>2</td>
<td>tetrahydrofuran/H₂O: 10/1</td>
<td>24</td>
<td>44 (S)</td>
</tr>
<tr>
<td>3</td>
<td>toluene/H₂O: 10/1</td>
<td>17</td>
<td>44 (S)</td>
</tr>
<tr>
<td>4</td>
<td>1,2-dimethoxyethane/H₂O: 10/1</td>
<td>45</td>
<td>30 (S)</td>
</tr>
<tr>
<td>5</td>
<td>2-propanol</td>
<td>&gt; 99</td>
<td>52 (S)</td>
</tr>
<tr>
<td>6</td>
<td>ethanol</td>
<td>&gt; 99</td>
<td>50 (S)</td>
</tr>
<tr>
<td>7</td>
<td>1,4-dioxane (dry)</td>
<td>87</td>
<td>36 (S)</td>
</tr>
<tr>
<td>8</td>
<td>tetrahydrofuran (dry)</td>
<td>31</td>
<td>42 (S)</td>
</tr>
<tr>
<td>9</td>
<td>toluene (dry)</td>
<td>26</td>
<td>20 (S)</td>
</tr>
<tr>
<td>10</td>
<td>1,2-dimethoxyethane (dry)</td>
<td>71</td>
<td>25 (S)</td>
</tr>
<tr>
<td>11</td>
<td>diisopropylether (dry)</td>
<td>90</td>
<td>50 (S)</td>
</tr>
<tr>
<td>12</td>
<td>n-heptane (dry)</td>
<td>58</td>
<td>51 (S)</td>
</tr>
<tr>
<td>13</td>
<td>1,2-dichloroethane (dry)</td>
<td>6</td>
<td>13 (S)</td>
</tr>
<tr>
<td>14&lt;sup&gt;e&lt;/sup&gt;</td>
<td>propionitrile (dry)</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reactions were carried out on 0.2 mmol scale in 2 mL of solvent at reflux for 4 h with 3 equiv of phenylboronic acid in the presence of a catalyst generated from 3 mol% Rh(acac)(C₂H₄)₂ and 7.5 mol% of phosphoramidite (S)-L₁.  
<sup>b</sup> Conversion determined by ¹H-NMR after work-up with 12.5% aqueous ammonia.  
<sup>c</sup> Determined by chiral HPLC.  
<sup>d</sup> The absolute configuration was established by comparison of the optical rotation with literature values (see experimental part).  
<sup>e</sup> Gives no conversion, probably due to coordination of the solvent to the catalyst.
Scheme 4.4 Proposed mechanism for the rhodium-catalyzed 1,2-addition of boronic acids to benzaldehydes

The presence of 6 suggests that, under these conditions, the alkoxide functionality of species D is able to induce the transmetallation step between arylboronic acids and the rhodium center. Due to the equilibria between phenylboronic acid and its boroxine trimer, the water content cannot be defined. The direct protonation of D by traces of water originating from the arylboronic acid remains possible. Also the formation of 6 from the product and boronic acid during the reaction cannot be excluded, although the 5a/6 ratio increased during the course of the reaction, pointing at slow hydrolysis of borate ester 6. Because of the protic nature of 2-propanol, 6 is not observed in this case and quenching with aqueous ammonia was not required in order to obtain the desired product.

4.2.2 Ligand Library Approach

A diverse library of ligands L-[x,y] with different substituents at the amine moiety can easily be obtained by an automated divergent synthesis via the phosphorochloridite 8, which can be readily prepared from BINOL (7) and an excess of PCl₃ (see Scheme 4.5).28
Table 4.2  Phosphoramidite Library (S)-L-[x,y] \(^a\)

<table>
<thead>
<tr>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>Y</td>
<td>X</td>
<td>Y</td>
</tr>
<tr>
<td>1</td>
<td>(\text{O}^{\text{H}})</td>
<td>(R)</td>
<td>(\text{O}^{\text{H}})</td>
</tr>
<tr>
<td>2</td>
<td>(\text{O}^{\text{H}})</td>
<td>(R)</td>
<td>(\text{O}^{\text{H}})</td>
</tr>
<tr>
<td>3</td>
<td>(\text{O}^{\text{Bn}})</td>
<td>((R,R))</td>
<td>(\text{O}^{\text{Bn}})</td>
</tr>
<tr>
<td>4</td>
<td>(\text{O}^{\text{Ph}})</td>
<td>(\text{O}^{\text{Bn}})</td>
<td>(\text{O}^{\text{Pr}})</td>
</tr>
<tr>
<td>5</td>
<td>(\text{O}^{\text{Bn}})</td>
<td>(\text{O}^{\text{Bn}})</td>
<td>(\text{O}^{\text{Bn}})</td>
</tr>
<tr>
<td>6</td>
<td>(\text{O}^{\text{Ph}})</td>
<td>(\text{O}^{\text{Bn}})</td>
<td>(\text{O}^{\text{Bn}})</td>
</tr>
<tr>
<td>7</td>
<td>(\text{O}^{\text{Bn}})</td>
<td>(\text{O}^{\text{Bn}})</td>
<td>(\text{O}^{\text{Bn}})</td>
</tr>
<tr>
<td>8</td>
<td>(\text{O}^{\text{Bn}})</td>
<td>(\text{O}^{\text{Bn}})</td>
<td>(\text{O}^{\text{Bn}})</td>
</tr>
</tbody>
</table>

\(^a\) All ligands were derived from (S)-BINOL 7.
The parallel solution phase synthesis and *in situ* screening of a library of BINOL-based phosphoramidites ($L$-[x,y], Table 4.2) was performed. In order to create a ligand library which could be used for lead-finding, a large variety of amines was used. In addition to 28 monodentate ligands, also 2 bidentate ligands were tested. A stock solution of phosphorochloridite (S)-8 in toluene was added to 30 positions of a 96-well oleophobic filterplate. The subsequent addition of a stoichiometric amount of triethylamine to each of these wells was followed by the addition of a stoichiometric amount of the corresponding amine in the case of a monodentate ligand or 0.5 equiv of diamine in the case of a bidentate ligand. After 2 h of agitation at room temperature on an orbital shaker, the precipitated triethylamine hydrochloric acid salts were removed via parallel filtration. By placing the oleophobic filterplate on top of a 96-well microplate and applying a vacuum, a ligand library of 30 clear stock solutions of phosphoramidites in toluene was obtained.

![Scheme 4.5 Divergent synthesis of BINOL (7) based phosphoramidites](image)

Using the liquid handling robot, part of the stock solution in each well of the library was transferred to 30 corresponding reaction vials in an aluminum heating block, followed by a 2-propanol stock solution of the rhodium precursor. Interestingly, the ligands that were not fully formed gave an orange to red colored solution on addition of the rhodium, whereas in all other cases the color of the solution was bright yellow, thus providing a color-indicator test for the success of ligand formation. It was confirmed that the red color is caused by the combination of the remaining phosphorochloridite 8 and Rh(acac)(C_2H_4)_2. After the addition of stock-solutions of substrate 4a (0.1 mmol) and phenylboronic acid (3 equiv) in 2-propanol, the vials were sealed and heated overnight at reflux temperature.
**Table 4.3** Enantioselectivities obtained from the library screening of phosphoramidite ligands in the phenylboronic acid addition to 4a

<table>
<thead>
<tr>
<th>L-[x,y]</th>
<th>ee (%)b,c</th>
<th>L-[x,y]</th>
<th>ee (%)b,c</th>
<th>L-[x,y]</th>
<th>ee (%)b,c</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-[1,1]</td>
<td>17 (S)</td>
<td>L-[2,2]</td>
<td>20 (S)</td>
<td>L-[3,6]</td>
<td>27 (S)</td>
</tr>
<tr>
<td>L-[1,2]</td>
<td>19 (S)</td>
<td>L-[2,4]</td>
<td>18 (S)</td>
<td>L-[3,7]</td>
<td>47 (S)</td>
</tr>
<tr>
<td>L-[1,3]</td>
<td>28 (S)</td>
<td>L-[2,5]</td>
<td>27 (S)</td>
<td>L-[3,8]</td>
<td>19 (R)</td>
</tr>
<tr>
<td>L-[1,4]</td>
<td>20 (S)</td>
<td>L-[2,6]</td>
<td>25 (S)</td>
<td>L-[4,1]</td>
<td>28 (S)</td>
</tr>
<tr>
<td>L-[1,5]</td>
<td>32 (S)</td>
<td>L-[2,7]</td>
<td>21 (S)</td>
<td>L-[4,2]</td>
<td>13 (S)</td>
</tr>
<tr>
<td>L-[1,6]</td>
<td>29 (S)</td>
<td>L-[3,1]</td>
<td>32 (S)</td>
<td>L-[4,3]</td>
<td>51 (S)</td>
</tr>
<tr>
<td>L-[1,7]</td>
<td>27 (S)</td>
<td>L-[3,2]</td>
<td>28 (S)</td>
<td>L-[4,4]</td>
<td>15 (S)</td>
</tr>
<tr>
<td>L-[1,8]</td>
<td>51 (R)</td>
<td>L-[3,3]</td>
<td>20 (S)</td>
<td>L-[4,5]</td>
<td>29 (S)</td>
</tr>
<tr>
<td>L-[2,1]</td>
<td>18 (S)</td>
<td>L-[3,4]</td>
<td>33 (S)</td>
<td>L-[4,6]</td>
<td>28 (S)</td>
</tr>
<tr>
<td>L-[2,3]</td>
<td>16 (S)</td>
<td>L-[3,5]</td>
<td>21 (S)</td>
<td>L-[4,7]</td>
<td>21 (S)</td>
</tr>
</tbody>
</table>

a Reactions were carried out on 0.1 mmol scale in 2 mL of solvent at reflux with 3 equiv of phenylboronic acid in the presence of a catalyst generated from 5 mol% Rh(acac)(C2H4)2 and 12.5 mol% of monodentate phosphoramidite or 6.25 mol% of bidentate phosphoramidite. b Determined by chiral HPLC. c The absolute configuration was established by comparison of the optical rotation with literature values (see § 4.5).

**Figure 4.2** Most successful ligands resulting from the library approach
Enantioselective Synthesis of Diarylmethanols

Chiral HPLC analysis of the reaction mixtures showed that most of the ligands gave rise to enantioselectivities below 40% and therefore did not exceed the results obtained by Miyaura (Table 4.3). However, the monodentate ligands based on indoline (L-[3,7]) and 1,2,3,4-tetrahydroquinoline (L-[4,3]) provided 47% and 51% ee, respectively (Figure 4.2). Also bidentate ligand L-[1,8] provided the product 5a in 51% ee. Interestingly, the bidentate ligands based on (S)-BINOL provide the (R)-enantiomer of the product, whereas the monodentate ligands provide the (S)-enantiomer.

In order to establish the validity of our protocol, the results of 18 representative library ligands were compared with the corresponding phosphoramidites that were synthesized manually and purified by column chromatography (Table 4.4). In general, the enantioselectivities provided by the unpurified solution phase ligands were accurate within a 4% error-margin. Although the enantioselectivities obtained with the most successful monodentate ligands L-[3,7] and L-[4,3] could be confirmed by these experiments, the value obtained with isolated bidentate ligand L-[1,8] was significantly higher. The reaction went to full conversion within 4 h, providing 5a with 60% ee. Also in the case of ligand L-[2,6], prepared from the relatively bulky benzyl(t-butyl)amine, the actual enantioselectivity is higher than the value indicated by the library. $^{31}$P-NMR spectra of the solution phase library shows that the phosphoramidites were generally obtained with over 90% purity (varying amounts of hydrolyzed ligand were observed). However, bidentate ligand L-[1,8] was not completely formed and contained a considerable amount of the monodentate phosphoramidite 9 (Scheme 4.6).

![Scheme 4.6 Formation of monodentate phosphoramidite 9 as side product](image-url)
Table 4.4 Comparison of results obtained with in situ prepared phosphoramidite ligands in the solution phase library with those obtained with isolated ligands

<table>
<thead>
<tr>
<th>L-[x,y]</th>
<th>ee b</th>
<th>ee c</th>
<th>L-[x,y]</th>
<th>ee b</th>
<th>ee c</th>
<th>L-[x,y]</th>
<th>ee b</th>
<th>ee c</th>
</tr>
</thead>
<tbody>
<tr>
<td>L-[1,6]</td>
<td>29%</td>
<td>25%</td>
<td>L-[3,2]</td>
<td>28%</td>
<td>31%</td>
<td>L-[4,1]</td>
<td>28%</td>
<td>29%</td>
</tr>
<tr>
<td>L-[1,8]</td>
<td>51%</td>
<td>60%</td>
<td>L-[3,3]</td>
<td>20%</td>
<td>22%</td>
<td>L-[4,3]</td>
<td>51%</td>
<td>51%</td>
</tr>
<tr>
<td>L-[2,2]</td>
<td>20%</td>
<td>21%</td>
<td>L-[3,4]</td>
<td>33%</td>
<td>31%</td>
<td>L-[4,4]</td>
<td>15%</td>
<td>18%</td>
</tr>
<tr>
<td>L-[2,4]</td>
<td>18%</td>
<td>18%</td>
<td>L-[3,6]</td>
<td>27%</td>
<td>30%</td>
<td>L-[4,5]</td>
<td>29%</td>
<td>29%</td>
</tr>
<tr>
<td>L-[2,6]</td>
<td>25%</td>
<td>36%</td>
<td>L-[3,7]</td>
<td>47%</td>
<td>48%</td>
<td>L-[4,6]</td>
<td>28%</td>
<td>30%</td>
</tr>
<tr>
<td>L-[3,1]</td>
<td>32%</td>
<td>33%</td>
<td>L-[3,8]</td>
<td>19%</td>
<td>18%</td>
<td>L-[4,7]</td>
<td>21%</td>
<td>24%</td>
</tr>
</tbody>
</table>

* Enantioselectivities were determined by chiral HPLC of the reaction mixtures. Reactions were carried out overnight in 2 mL of 2-propanol at reflux temperature; 3 equiv of phenylboronic acid were used. b Reactions were performed on 0.1 mmol scale in the presence of a catalyst generated from 3 mol% Rh(acac)(C₂H₄)₂ and 7.5 mol% of monodentate phosphoramidite or 3.75 mol% of bidentate phosphoramidite. c Reactions were carried out on 0.1 mmol scale in the presence of a catalyst generated from 5 mol% Rh(acac)(C₂H₄)₂ and 12.5 mol% of monodentate phosphoramidite or 6.25 mol% of bidentate phosphoramidite.
After the first phosphorochloridite unit reacts with the diamine, the second amine functionality seems to compete with triethylamine for the formation of a salt with the liberated HCl. The phosphoramidite salt is partly soluble in toluene and is, therefore, not completely removed upon filtration. This results in a mixture of bidentate and monodentate phosphoramidite ligands with a depletion in stereoselectivity by the monodentate ligands present. Also in the case of bulky amines the corresponding phosphoramidites (L-[2,6], L-[2,3], and L-[3,2]) were only partially formed, showing a limitation of the current methodology. Ligand L-[4,2], based on the rather unreactive δ-valerolactam, was not formed at all.

### 4.2.3 Scope of the Reaction

The rhodium-catalyzed arylation of aldehydes is compatible with a wide range of functional groups (Table 4.5). As already observed by Miyaura and Frost, the reaction is rather sensitive to electronic effects both in aldehyde and arylboronic acid. Moreover, it was observed that a product with multiple electron-donating substituents on the aryl moiety, like 3,4-dimethoxybenzaldehyde 4h (entry 10) can undergo $S_N^1$ substitution by the solvent 2-propanol, resulting in the corresponding racemic ether 10 (Scheme 4.7).

![Scheme 4.7 1,2-Addition of phenylboronic acid to 4h followed by $S_N^1$ substitution](image)

Phenylation of benzaldehydes with electron-withdrawing chloro- and trifluoromethyl-substituents at the para-position gave the corresponding alcohols 5a and 5b in high yields with 60% and 51% enantioselectivity, respectively (entries 1 and 2). In case of a $p$-phenyl group, the product could be isolated in 93% yield with 59% ee (entry 3). Substrates with electron-donating methoxy- and methyl-substituents at the para-position both provided 60% ee, but did not proceed to full conversion in 4 h (entries 4 and 5).
Chapter 4

Table 4.5 Scope of the rhodium/L-[1,8] catalyzed addition of Ar\textsuperscript{2}B(OH)\textsubscript{2} to aldehydes

\[
\begin{align*}
\text{Ar}^1\text{H} & + \text{Ar}^2\text{B(OH)}\text{2} (3 \text{ equiv}) \\
\text{Rh(acac)(C} \text{}_2\text{H}_4\text{)}\text{2} (3 \text{ mol%}) & \quad \text{2-propanol, reflux, 4 h} \\
\text{Ar}^1\text{B(OH)}\text{2Ar}^2 & \quad \text{(S,S)-L-[1,8]} (3.5 \text{ mol%}) \\
\end{align*}
\]

<table>
<thead>
<tr>
<th>entry\textsuperscript{a}</th>
<th>substrate (Ar\textsuperscript{1})</th>
<th>Ar\textsuperscript{2}</th>
<th>product</th>
<th>yield (%)\textsuperscript{b}</th>
<th>ee (%)\textsuperscript{c,d}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4a (p-(Cl)C\textsubscript{6}H\textsubscript{4})</td>
<td>Ph</td>
<td>5a</td>
<td>91</td>
<td>60 ((R))</td>
</tr>
<tr>
<td>2</td>
<td>4b (p-(CF\textsubscript{3})C\textsubscript{6}H\textsubscript{4})</td>
<td>Ph</td>
<td>5b</td>
<td>94</td>
<td>51 ((R))</td>
</tr>
<tr>
<td>3</td>
<td>4c (p-(Ph)C\textsubscript{6}H\textsubscript{4})</td>
<td>Ph</td>
<td>5c</td>
<td>93</td>
<td>59 ((R))</td>
</tr>
<tr>
<td>4</td>
<td>4d (p-(Me)C\textsubscript{6}H\textsubscript{4})</td>
<td>Ph</td>
<td>5d</td>
<td>80</td>
<td>60 ((R))</td>
</tr>
<tr>
<td>5</td>
<td>4e (p-(MeO)C\textsubscript{6}H\textsubscript{4})</td>
<td>Ph</td>
<td>5e</td>
<td>61</td>
<td>60 ((R))</td>
</tr>
<tr>
<td>6</td>
<td>4f (Ph)</td>
<td></td>
<td>5d</td>
<td>93</td>
<td>47 ((S))</td>
</tr>
<tr>
<td>7</td>
<td>4f (Ph)</td>
<td>2-naphthyl</td>
<td>5f</td>
<td>92</td>
<td>53 ((S))</td>
</tr>
<tr>
<td>8</td>
<td>4g (m-(MeO)C\textsubscript{6}H\textsubscript{4})</td>
<td>Ph</td>
<td>5g</td>
<td>96</td>
<td>61 ((R))</td>
</tr>
<tr>
<td>9\textsuperscript{e}</td>
<td>4h (m,p-(MeO)\textsubscript{2}C\textsubscript{6}H\textsubscript{4})</td>
<td>Ph</td>
<td>10</td>
<td>92</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>4i (o-(MeO)C\textsubscript{6}H\textsubscript{4})</td>
<td>Ph</td>
<td>5i</td>
<td>89</td>
<td>50 ((R))</td>
</tr>
<tr>
<td>11\textsuperscript{f}</td>
<td>4j (o-(Br)C\textsubscript{6}H\textsubscript{4})</td>
<td>Ph</td>
<td>5j</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>12\textsuperscript{f}</td>
<td>4k (2-pyridyl)</td>
<td>Ph</td>
<td>5k</td>
<td>nd</td>
<td>nd</td>
</tr>
<tr>
<td>13</td>
<td>4l (1-naphthyl)</td>
<td>Ph</td>
<td>5l</td>
<td>67</td>
<td>52 ((R))</td>
</tr>
<tr>
<td>14</td>
<td>4m (2-naphthyl)</td>
<td>Ph</td>
<td>5m</td>
<td>92</td>
<td>75 ((R))</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Reactions were carried out on 0.2 mmol scale in 2 mL of 2-propanol at reflux for 4 h with 3 equiv of boronic acid in the presence of a catalyst generated from 3 mol% Rh(acac)(C\textsubscript{2}H\textsubscript{4})\textsubscript{2} and 3.5 mol% of bidentate phosphoramidite (S,S)-L-[1,8]. \textsuperscript{b} Isolated yields after column chromatography on silica gel (n-heptane/EtOAc: 15/1). \textsuperscript{c} Determined by chiral HPLC. \textsuperscript{d} The absolute configuration was established by comparison of the optical rotation with literature values or deduced by analogy (see experimental section). \textsuperscript{e} S\textsubscript{N}1 substitution of 5h with 2-propanol took place, resulting in the corresponding racemic ether 10. \textsuperscript{f} Not determined: no conversion was observed.
The alternative reaction of benzaldehyde with substituted arylboronic acids did give high yields, but showed decreased enantioselectivities (entries 6 and 7). A slightly lower ee and reactivity was observed for sterically hindered substrates like \( o \)-methoxy benzaldehyde (entry 9) and \( 1 \)-naphthyl carboxaldehyde (entry 13).

Addition of phenylboronic acid to the even more hindered \( o \)-bromo benzaldehyde (entry 11) did not proceed. The addition to picolinaldehyde (2-pyridyl carboxaldehyde, entry 12) did not give any product either. It is proposed that the substrate complexates to rhodium too strongly and blocks the catalyst in this way. The best enantioselectivity was obtained with \( 2 \)-naphthyl carboxaldehyde, which could be phenylated in 92% isolated yield with an ee of 75% (entry 14, see Scheme 4.8).

### 4.3 Further Developments

Almost simultaneous with the publication of our results on this subject, Zhou et al. reported a rhodium-catalyst for the addition of arylboronic acids to benzaldehydes employing chiral phosphite \( \text{L2} \) (Figure 4.3) based on SPINOL (1,1'-spirobiindane-7.7'-diol).
Chapter 4

This class of ligands, developed by the group of Zhou, was previously reported to be highly efficient in asymmetric rhodium-catalyzed hydrogenation, copper-catalyzed asymmetric ring-opening reactions of bicyclic alkenes with Grignard reagents, palladium-catalyzed allylation of aldehydes, and other asymmetric reactions. Diarylmethanols were obtained in high isolated yields, for a variety of arylboronic acids and benzaldehydes, regardless of the electronic nature of the substituents on either reagent. Enantioselectivities ranged from 62% up to 87%. In contrast to our system, here the use of ortho-substituted benzaldehydes as substrates increases the enantioselectivity, rendering both systems complementary to each other.

4.4 Conclusions

In summary, a ligand library approach to the development of new catalysts for the asymmetric addition of arylboronic acids to benzaldehydes has resulted in a new rhodium/phosphoramidite-system that provides diarylmethanols with high isolated yields (up to 96%) and good enantioselectivities (up to 75%). Further optimization of the system might be accomplished by variation of the bidentate ligand structure in both the diamine backbone and the BINOL-moiety.

4.5 Experimental Section

General remarks: For general information, see Chapter 2. Ligand libraries were synthesized using a Zinsser Lissy liquid handling robot equipped with 4 probes and placed inside a glove box. Whatman PKP 2 mL 96-well filter plates in combination with the UniVac 3 vacuum manifold were used to perform the parallel filtration of the ligand library. Screening of the ligand libraries was performed in a parallel reactor consisting of an aluminum block on a magnetical stirrer/heater containing 32 10 mL vials equipped with magnetic stirring bar, screwcap, and septum. Phosphoramidite ligands were prepared according to a literature procedure. Spectral data for L1 can be found in reference 23a. Spectral data for L-[3,3], L-[3,6], L-[3,7], L-[4,3], L-[4,4], and L-[4,5] can be found in
Enantioselective Synthesis of Diarylmethanols

reference 22a. Spectral data for L-[2,2] can be found in reference 22b. Spectral data for L-[1,8], L-[2,4], L-[3,1], L-[3,2], L-[3,4], L-[4,1], L-[4,5], L-[4,6], and L-[4,7] can be found in reference 22c. Spectral data for L-[2,6] can be found in reference 35. Spectral data for L-[3,8] can be found in reference 36. A procedure for the preparation of L-[1,6], including spectral data, can be found in Chapter 5.

**General procedure for solvent screening Table 4.1, entries 1-14.** In a flame dried Schlenk tube flushed with nitrogen 1.55 mg (6.0 µmol, 3 mol%) of Rh(acac)(C₂H₄)₂ and 14.0 µmol (7.5 mol%) of one of the enantiomers of phosphoramidite L₁ were dissolved in 2 mL of solvent. After stirring for 15 min at room temperature, 0.2 mmol of substrate 4a and 0.6 mmol of phenylboronic acid (3 equiv) were added and the resulting mixture was stirred at reflux. After 4 h the reaction mixture was cooled to RT and quenched with 2 mL of a 12.5% aqueous ammonia solution. After 20 min the water-layer was extracted with 3 x 5 mL of ethylacetate, the combined organic layers dried on Na₂SO₄, and the solvent evaporated under reduced pressure.

**Identification of borate ester 6a.** In a flame dried Schlenk tube flushed with nitrogen, 1.55 mg (6.0 µmol, 3 mol%) of Rh(acac)(C₂H₄)₂ and 14.0 µmol (7.5 mol%) of one of the enantiomers of phosphoramidite L₁ were dissolved in 2 mL of dry dioxane. After stirring for 15 min at room temperature, 0.2 mmol of substrate 4a and 0.4 mmol of phenylboronic acid (2 equiv) were added and the resulting mixture was stirred at reflux. After 4 h the reaction mixture was cooled to RT. The reaction mixture was passed through a silica-plug and the solvent evaporated under reduced pressure. According to ¹H-NMR, a mixture was obtained consisting of 9% starting material 4a, 36% product 5a, and 55% borate ester 6a with a characteristic benzydrylic proton signal at 6.21 ppm. Negative ion ESI-MS using diluted NH₃ (aq.) as a base, gave a specific isotope pattern for C₁₂H₁₁BO₃·NH₃ (M-NH₄⁺): m/z 277.1 (15%, ¹⁰B, ³⁵Cl), 278.1 (100%, ¹¹B, ³⁵Cl), 279.0 (25%, ¹⁰B, ³⁷Cl), 280.0 (25%, ¹¹B, ³⁷Cl). Usual work-up of the mixture with aqueous ammonia 12.5% (*vide supra*), hydrolyzing 6a, followed by flash chromatography (SiO₂, pentane/EtOAc: 20/1) gave the product 5a in 89% isolated yield.
Phosphorochloridite (S)-8. To a Schlenk vessel containing 3.0 g (10.5 mmol) of (S)-bis-β-naphthol 12 mL of PCl₃ was added. The resulting suspension was refluxed overnight and the excess PCl₃ was removed in vacuo. Anhydrous toluene (3 x 5 mL) was added and the remaining PCl₃ was removed by azeotropic distillation to give a white foam after thorough removal of all volatiles under high vacuum. The resulting phosphorochloridite 8 was obtained in quantitative yield (3.6 g, 10.5 mmol). ¹H NMR (CDCl₃) δ = 8.01 (m, 4H), 7.56 (m, 8H); ³¹P NMR δ = 177.6.

General procedure for the automated synthesis of ligand library L-[x,y], Table 4.2. The preparation of ligand libraries was adapted from a previously reported procedure. Stock solutions were prepared by dissolving the proper amounts of every reagent necessary for the library synthesis in dry toluene (all by weight). For the phosphorochloridite and the triethylamine a concentration of 0.5 M was used. In the case of monodentate ligands, 1.0 M stock solutions of the corresponding amines were prepared. In the case of bidentate ligands, 0.5 M stock solutions of the corresponding diamines were prepared. Using the liquid handling robot, 100 µL of the phosphorochloridite solution and 100 µL of the triethylamine solution were transferred into each of 30 wells of the Whatman PKP filter plate. Next, 50 µL of each of the 30 amine solutions was added to the corresponding well. The microplate was placed on an orbital shaker and vortexed for 2 h at room temperature. The microplate was then placed onto the vacuum manifold and filtration was performed upon application of vacuum. The filtrates, i.e. 30 solutions of different ligands in dry toluene, were collected and stored into a 96-well polypropylene microplate.

General procedure for the automated in situ screening of library L-[x,y], Table 4.3. Stock solutions were prepared in 2-propanol containing the rhodium precursor, Rh(acac)(C₂H₄)₂ at a concentration of 0.05 M, and the substrate 4a at a concentration of 0.05 M. Using the liquid handling robot 62.5 µL of the ligand solutions (12.5 µmol for monodentate ligands and 6.25 µmol for bidentate ligands) was transferred from the microplate into 30 vials, equipped with stirring bars. Then 100 µL of the Rh(acac)(C₂H₄)₂ (5.0 µmol) and 2 mL of 4a stock solution (0.1 mmol) was added to each of the 30 vials.

80
After the addition of 36.3 mg (0.3 mmol) of phenylboronic acid the vials were capped and transferred to the parallel reactor. The reaction mixtures were left stirring overnight at reflux. After evaporating the solvent, the obtained solids were analyzed by chiral HPLC (vide infra) in order to determine the enantiomeric excess.

**General procedure for substrate scope experiments** Table 4.5, entries 1-14. In a flame dried Schlenk tube flushed with nitrogen, 1.55 mg (6.0 µmol, 3 mol%) of Rh(acac)(C\(_2\)H\(_4\)) and 6.5 µmol (3.5 mol%) phosphoramidite (S,S)-L-[1,8] were dissolved in 2 mL of 2-propanol. After stirring for 15 min at room temperature, 0.2 mmol of substrate 4 and 0.6 mmol of arylboronic acid (3 equiv) were added and the resulting mixture was stirred at reflux. After 4 h the reaction mixture was cooled to RT and evaporated under reduced pressure. Products were purified by flash chromatography (SiO\(_2\), pentane/EtOAc: 20/1).

(R)-(4-Chlorophenyl)phenylmethanol (5a). Obtained as a solid (mp 47.4-48.4 °C) in 91% isolated yield with 60% ee (Table 4.5, entry 1). The ee was determined on a Chiracel AD column with n-heptane/2-propanol: 95/5, flow = 1.0 mL/min. Retention times: 11.3 [(R)-enantiomer] and 12.1 [(S)-enantiomer] min. \([\alpha]\)\(^{20}\)\(_D\) = -10.4 (c 1.08, CHCl\(_3\), 60%), lit.\(^{37}\) \([\alpha]\)\(^{20}\)\(_D\) = -18.6 (c 0.86, CHCl\(_3\), 94% ee, (R)); \(^1\)H NMR (CDCl\(_3\)) \(\delta = 7.21-7.30\) (m, 9H), 5.75 (s, 1H), 2.11 (bs, 1H); \(^13\)C NMR (CDCl\(_3\)) \(\delta = 143.40, 142.17, 133.25, 128.62, 128.57, 127.84, 126.49, 75.59; HRMS calcd for C\(_{13}\)H\(_{11}\)O\(_3\)Cl: m/z 220.0469, found: 220.0461.

(R)-(4-Trifluoromethylphenyl)phenylmethanol (5b). Obtained as a solid (mp 71.9-73.0 °C) in 94% isolated yield with 51% ee (Table 4.5, entry 2). The ee was determined on a Chiracel AD column with n-heptane/2-propanol: 98/2, flow = 1.0 mL/min. Retention times: 17.0 [(R)-enantiomer] and 20.2 [(S)-enantiomer] min. \([\alpha]\)\(^{20}\)\(_D\) = -19.4 (c 1.05, CHCl\(_3\), 51% ee), lit.\(^{26}\) \([\alpha]\)\(^{20}\)\(_D\) = -34.6 (c 0.19, C\(_6\)H\(_6\), 94% ee, (R)) \(^1\)H NMR (CDCl\(_3\)) \(\delta = 7.45-7.56\) (m, 4H), 7.21-7.31 (m, 5H), 5.83 (s, 1H), 2.19 (bs, 1H); \(^13\)C NMR (CDCl\(_3\)) \(\delta = 147.48, 143.13, 129.21\) (q, \(J\)\(_{CF}\) = 32.1 Hz), 128.75, 128.08, 126.64, 126.61, 125.39 (q, \(J\)\(_{CF}\) = 3.7 Hz), 124.19 (q, \(J\)\(_{CF}\) = 286.4 Hz), 75.75; HRMS calcd for C\(_{14}\)H\(_{11}\)OF\(_3\): m/z 252.0762, found: 252.0774.
Chapter 4

(R)-(4-Phenylphenyl)phenylmethanol (5c). Obtained as a solid (mp 74.0-74.6 °C) in 93% isolated yield with 59% ee (Table 4.5, entry 3). The ee was determined on a Chiralcel AD column with n-heptane/2-propanol: 98/2, flow = 1.0 mL/min. Retention times: 36.8 [(S)-enantiomer] and 41.9 [(R)-enantiomer] min. The absolute configuration was assigned by analogy. \([\alpha]_D^{19} = -3.2 (c 1.01, \text{CHCl}_3, 59\% \text{ ee})\); \(^1\)H NMR (CDCl\(_3\)) \(\delta = 7.21-7.57\) (m, 14H), 5.84 (s, 1H), 2.38 (bs, 1H); \(^13\)C NMR (CDCl\(_3\)) \(\delta = 143.69, 142.77, 140.71, 140.41, 128.71, 128.50, 127.57, 127.23, 127.18, 127.02, 126.93, 126.51, 75.96; HRMS c alc. for C\(_{19}\)H\(_{16}\)O: m/z 260.1201, found: 260.1203.

(R)- and (S)-(4-Tolyl)phenylmethanol (5d). The (R)-enantiomer was obtained as a solid (mp 51.4-52.9 °C) in 80% isolated yield with 60% ee (Table 4.5, entry 4) and the (S)-enantiomer was obtained as a solid in 93% isolated yield with 47% ee (Table 4.5, entry 6). The ee was determined on a Chiralcel AD column with n-heptane/2-propanol: 98/2, flow = 1.0 mL/min. Retention times: 20.6 [(R)-enantiomer] and 21.7 [(S)-enantiomer] min. \([\alpha]_D^{21} = +5.2 (c 0.92, \text{CHCl}_3, 60\% \text{ ee}), [\alpha]_D^{20} = -4.0 (c 0.76, \text{CHCl}_3, 47\% \text{ ee}), \text{lit.}^{38} [\alpha]_D^{20} = +8.4 (c 0.50, \text{CHCl}_3, 97\% \text{ ee}, (R)); \(^1\)H NMR (CDCl\(_3\)) \(\delta = 7.09-7.33\) (m, 9H), 5.76 (s, 1H), 2.29 (s, 3H), 2.19 (bs, 1H); \(^13\)C NMR (CDCl\(_3\)) \(\delta = 143.89, 140.90, 137.22, 129.13, 128.39, 127.40, 126.47, 126.40, 76.03, 21.07; HRMS calc. for C\(_{14}\)H\(_{14}\)O: m/z 198.1045, found: 198.1053.

(R)-(4-Methoxyphenyl)phenylmethanol (5e). Obtained as a viscous oil in 61% isolated yield with 60% ee (Table 4.5, entry 5). The ee was determined on a Chiralcel AD column with n-heptane/2-propanol: 95/5, flow = 1.0 mL/min. Retention times: 16.7 [(R)-enantiomer] and 17.8 [(S)-enantiomer] min. \([\alpha]_D^{20} = +16.9 (c 0.44, \text{C}_6\text{H}_6, 60\% \text{ ee}), \text{lit.}^{39} [\alpha]_D^{20} = +18.7 (c 1.86, \text{C}_6\text{H}_6, (R)); \(^1\)H NMR (CDCl\(_3\)) \(\delta = 7.20-7.34\) (m, 7H), 6.82 (m, 2H), 5.76 (s, 1H), 3.74 (s, 3H), 2.20 (bs, 1H); \(^13\)C NMR (CDCl\(_3\)) \(\delta = 158.99, 143.96, 136.12, 128.40, 127.86, 127.38, 126.35, 113.82, 75.76, 55.24; HRMS calc. for C\(_{14}\)H\(_{14}\)O\(_2\): m/z 214.0994, found: 214.0992.
(R)- and (S)-(2-Naphthyl)phenylmethanol (5f). The (S)-enantiomer was obtained as a solid (mp 70.9-71.2 °C) in 92% isolated yield with 53% ee (Table 4.5, entry 7) and the (R)-enantiomer was obtained as a solid in 92% isolated yield with 75% ee (Table 4.5, entry 14). The ee was determined on a Chiralcel OD-H column with n-heptane/2-propanol: 90/10, flow = 0.5 mL/min. Retention times: 24.3 [S-enantiomer] and 28.0 [R-enantiomer] min. [$\alpha$]$_{2\varphi}$D = -4.8 (c 1.37, C$_6$H$_6$, 53% ee), [$\alpha$]$_{2\varphi}$D = +6.7 (c 1.62, C$_6$H$_6$, 75% ee), lit.$^{39}$ [$\alpha$]$_{2\varphi}$D = +7.4 (c 0.76, C$_6$H$_6$, 94% ee, (R)). $^1$H NMR (CDCl$_3$) δ = 7.75-7.85 (m, 4H), 7.20-7.47 (m, 8H), 5.95 (s, 1H), 2.36 (bs, 1H); $^{13}$C NMR (CDCl$_3$) δ = 143.59, 141.09, 133.22, 132.85, 128.51, 128.29, 128.04, 127.64, 126.68, 126.15, 125.94, 125.00, 124.74, 76.32; HRMS calcd for C$_{17}$H$_{14}$O: m/z 234.1045, found: 234.1051.

(R)-(3-Methoxyphenyl)phenylmethanol (5g). Obtained as an oil in 96% isolated yield with 61% ee (Table 4.5, entry 8). The ee was determined on a Chiralcel AD column with n-heptane/2-propanol: 98/2, flow = 1.0 mL/min. Retention times: 34.3 [(S)-enantiomer] and 36.0 [(R)-enantiomer] min. The absolute configuration was assigned by analogy. [$\alpha$]$_{2\varphi}$D = -8.7 (c 0.99, CHCl$_3$, 61% ee); $^1$H NMR (CDCl$_3$) δ = 7.19-7.35 (m, 6H), 6.90 (m, 2H), 6.77 (m, 1H), 5.74 (s, 1H), 3.74 (s, 3H), 2.38 (bs, 1H); $^{13}$C NMR (CDCl$_3$) δ = 159.64, 145.41, 143.61, 129.44, 128.42, 128.19, 127.52, 126.46, 118.84, 112.89, 112.02, 76.06, 55.14; HRMS calcd for C$_{14}$H$_{14}$O: m/z 214.0994, found: 214.1002.

(R)-(2-Methoxyphenyl)phenylmethanol (5i). Obtained as an oil in 89% isolated yield with 50% ee (Table 4.5, entry 10). The ee was determined on a Chiralcel AD column with n-heptane/2-propanol: 95/5, flow = 1.0 mL/min. Retention times: 13.1 [(S)-enantiomer] and 14.2 [(R)-enantiomer] min. [$\alpha$]$_{2\varphi}$D = +18.2 (c 0.77, CHCl$_3$, 50% ee); $^1$H NMR (CDCl$_3$) δ = 7.18-7.36 (m, 7H), 6.83-6.93 (m, 2H), 6.02 (s, 1H), 3.76 (s, 3H), 2.99 (bs, 1H); $^{13}$C NMR (CDCl$_3$) δ = 156.70, 143.24, 131.94, 128.67, 128.11, 127.82, 127.10, 126.51, 120.76, 110.73, 72.21, 55.36; HRMS calcd for C$_{14}$H$_{14}$O$_2$: m/z 214.0994, found: 214.1003.
(R)-(1-Naphthyl)phenylmethanol (5l). Obtained as a viscous oil in 67% isolated yield with 52% ee (Table 4.5, entry 13). The ee was determined on a Chiralcel AD column with n-heptane/2-propanol: 98/2, flow = 1.0 mL/min. Retention times: 35.1 [(S)-enantiomer] and 38.8 [(R)-enantiomer] min. $[\alpha]_{D}^{20} = +29.6$ (c 0.54, C6H6, Table 4, entry 13, 52% ee), lit. $[\alpha]_{D}^{20} = +59.5$ (c 0.88, C6H6, >98% ee, (R)). $^1$H NMR (CDCl3) $\delta$ = 7.99 (m, 1H), 7.74-7.85 (m, 2H), 7.59 (m, 1H), 7.21-7.47 (m, 8H), 6.49 (s, 1H), 2.16 (bs, 1H); $^{13}$C NMR (CDCl3) $\delta$ = 143.05, 138.73, 133.88, 130.63, 128.73, 128.50, 128.45, 128.29, 127.64, 127.00, 126.11, 125.94, 125.56, 125.29, 124.57, 124.94, 73.63; HRMS calcd for C17H14O: m/z 234.1045, found: 234.1053.

(+/-)-4-(Isopropoxy(phenyl)methyl)1,2-dimethoxybenzene (10). Obtained as a solid in 92% isolated yield (Table 4.5, entry 10). The ee was determined on a Chiralcel OD-H column with n-heptane/2-propanol: 90/10, flow = 0.5 mL/min. Retention times: 8.1 and 8.5 min. $^1$H NMR (CDCl3) $\delta$ = 7.23-7.31 (m, 5H), 6.74-6.86 (m, 3H), 5.39 (s, 1H), 3.80 (s, 3H), 3.62 (m, 1H) 1.18 (dd, J = 3.3, 2.8 Hz, 6H); $^{13}$C NMR (CDCl3) $\delta$ = 148.98, 148.26, 143.04, 135.49, 128.22, 127.15, 126.94, 119.55, 110.76, 110.18, 80.20, 69.04, 55.85, 55.77, 22.40, 22.11; HRMS calcd for C18H22O3: m/z 286.1653, found: 286.1569.

4.6 References and Notes

1. Patrick Y. Toullec is gratefully acknowledged for his assistance with the parallel synthesis and in situ screening of phosphoramidites described in this chapter. Laurent Lefort of DSM is gratefully acknowledged for useful discussions. We would like to thank Ebe Schudde for technical support.

Enantioselective Synthesis of Diarylmethanols


13. See Chapter 1, §1.4, for a more detailed discussion of this method. For recent examples, see: (a) J.-X. Ji, J. Wu, T. T.-L. Au-Yeung, C.-W. Yip, R. K. Haynes, A.
Chapter 4


Enantioselective Synthesis of Diarylmethanols

120, 5579. (c) For a recent review, see: T. Hayashi, K. Yamasaki, Chem. Rev. 2003, 103, 2829.


27. Borate ester 6 has a characteristic benzhydrylic proton signal in 1H-NMR at 6.21 ppm and was further identified by negative ion ESI-MS, which gave a specific isotope pattern for C10H17ClBO3N (M-NH4+): m/z 277.1 (15%, 10B, 35Cl), 278.1 (100%, 11B, 35Cl), 279.0 (25%, 10B, 37Cl), 280.0 (25%, 11B, 37Cl).


