New aspects of palladium-catalysed carbon-carbon bond formation reactions

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CHAPTER 4

Fast Asymmetric Intramolecular Heck Reactions using Chiral Bulky Monodentate Phosphoramidites: Origin of Enantioselectivity

Abstract

The application of chiral, monodentate phosphoramidite ligands based on bulky BINOL and TADDOL backbones gives rise to very rapid asymmetric intramolecular palladium-catalysed Heck reactions of aryl iodides under extremely mild conditions (room temperature or even lower). This high activity is caused by mono-coordination of the ligands, which leaves the transient palladium complexes coordinatively unsaturated. This mono-coordination is a consequence of the large steric bulk of the ligands, which hampers ligation of a second phosphoramidite during catalysis. The electron-withdrawing properties of the ligands further enhance the reaction rates in comparison with commonly used Pd-diphosphine catalysts. The enantioselectivities obtained using bulky TADDOL-based phosphoramidites are sensitive to structural variations in the ligand, reaching values of up to 79% ee in our model reaction using ligand (1R,7R)-4-Diethylamino-9,9-dimethyl-2,2,6,6-tetra(3,5-dimethylphenyl)-3,5,8,10-tetraoxa-4-phosphabicyclo[5.3.0]decane ((R,R)-5). The intermediate palladium(aryl)(halide) complexes exist as dimers and have been prepared and isolated. X-ray analysis of crystals obtained of complex [Pd((R,R)-5)(4-CNCH$_2$)$_2$][μ-Br]$_2$ confirms the dimeric structure and the mono-coordination of the ligand to palladium. These dimers act as the resting state of the catalyst during the reaction. The observed enantioselectivity presumably originates from a kinetic resolution mechanism, in which one of the enantiomers initially formed is more prone to dissociate from palladium to give the product, whereas the opposite enantiomer mainly undergoes reinsertion and (possibly multiple) isomerisation.

$^6$ To be submitted for publication: Maarten D. K. Boele, Gino P. F. van Strijdonck, Paul C. J. Kamer, Martin Lutz, Anthony L. Spek, Johannes G. de Vries and Piet W. N. M. van Leeuwen 2002
4.1 Introduction

The palladium-catalysed arylation or alkenylation of alkenes, better known as the Heck reaction, has emerged as an extremely powerful tool for the formation of new carbon-carbon bonds. As part of more recent developments, intramolecular Heck couplings have been employed successfully in many cases in constructing trisubstituted and even tetrasubstituted olefins or tertiary and quaternary carbon centres. Since the first reports in 1989 by Overman and Shibasaki, the asymmetric variant of the intramolecular Heck reaction has appeared as a crucial step in many asymmetric total syntheses of different natural products. Also, asymmetric intermolecular Heck couplings have been developed, although their potential for application in synthetic organic chemistry is far from being fully exploited yet.

The vast majority of the reported asymmetric Heck reactions uses bidentate diphosphine ligands or, in some cases, P-N ligands. Overman et al. have shown that the cyclization of α,β-unsaturated 2-halooamide derivatives can be performed with moderate to very high enantioselectivities using Pd BINAP as the catalyst. Moreover, the stereochemical outcome of the reaction can be steered by the addition of halide-scavengers to the reaction mixture. These observations have been rationalised in terms of different chiral inductions in the proposed cationic four-coordinate or neutral five-coordinate palladium-intermediates (with and without halide-scavenger present, respectively).

Unfortunately, these and other catalyst systems, which use bidentate diphosphines as auxiliaries, suffer from the drawback that the reactions are very slow. Therefore, prolonged reaction times together with elevated temperatures and high palladium-loadings are required to obtain acceptable conversions. In fact, it has been established earlier that generally diphosphines are not very suitable ligands for Heck reactions as they give low conversions, although examples exist in which diphosphines give good results. When functional groups are present in the substrate, the relatively harsh conditions can pose problems due to the possible occurrence of side-reactions. Therefore clearly a need exists for catalysts that provide high enantioselectivities combined with high activities under milder conditions.

Phosphoramidites form a class of ligands that, despite their high potential, have so far been relatively unexplored. The few early examples include the hydroformylation, as was shown in our group. An important breakthrough demonstrating the value of chiral phosphoramidites has been accomplished by Alexakis and Feringa and co-workers. They successfully applied BINOL-based phosphoramidites in the copper-catalysed asymmetric 1,4-addition, which gave excellent enantioselectivities in many cases. More recently, it has been shown that monodentate phosphoramidites can function as effective chiral auxiliaries in other metal-catalysed reactions, including hydrogenations, hydrostilbations and hydrovinylation reactions.
In Chapter 3, we demonstrated the application of bulky, monodentate phosphoramidites (for example 1) as effective and versatile ligands in intermolecular Heck reactions.[36] The resulting catalysts appeared to be extremely active in the reaction between alkenes and aryl iodides, even at room temperature. The crucial ligand properties for this remarkable performance is the bulkiness of the ligand, which prevents the coordination of more than one ligand to the metal centre, thereby rendering the complex coordinatively unsaturated. From kinetic studies it was shown that within

![Figure 1. Phosphoramidite successfully applied in Heck reactions.](image)

our model systems these catalysts behave well-defined, and that the oxidative addition is not the rate determining step of the catalytic cycle. Instead, the migratory insertion of the alkene into the Pd-aryl bond is rate limiting.[36, 37]

These results encouraged us to investigate the possibilities of performing very fast asymmetric Heck reactions using chiral bulky monodentate phosphoramidites. Moreover, application of these catalyst systems would enable the performance of Heck reactions under much milder conditions than usually applied nowadays. During the preparation of this manuscript, Feringa and co-workers reported high enantioselectivities in an intramolecular Heck reaction using monodentate phosphoramidites based on TADDOL backbones, showing the promising properties of this class of ligands.[38] The reactivity of the catalyst system still leaves room for improvement. In this chapter we present our results in this field, together with some important mechanistic considerations.
4.2 Results and Discussion

4.2.1 Ligand Synthesis

For a first screening we decided to use bulky diols based on BINOL (2,2'-dihydroxy-1,1'-binaphthyl) and TADDOL\(^{39}\) (2,3-O-isopropylidene-1,1,4,4-tetraphenyltreitol, or, more in general, \(\alpha,\alpha,\alpha',\alpha'-\text{tetraaryl}-2,2\text{-dimethyl}-1,3\text{-dioxolan}-4,5\text{-dimethanol}\)) backbones. These backbones offer the advantage of straightforward preparation and, importantly, allow a modular approach in ligand design. This modularity enables extensive fine-tuning of the ligand structures, meeting the needs of a particular substrate and/or reaction.

The chiral bulky phosphoramidites 2-13 were synthesised analogously to published methods\(^{28, 31, 40}\). Heating the appropriate diol with an equimolar amount of PCl\(_3\) in the presence of Et\(_3\)N, followed by reaction with the desired amine afforded the corresponding product, which was purified by column chromatography (SiO\(_2\)) (Scheme 1, route A). Ligands 2 and 4 were prepared by reaction of the corresponding diols with HMPT (hexamethylphosphorous triamide, route B in Scheme 1)\(^{41}\). The yields obtained were moderate to high. The ligands showed good stability in the

\[
\text{OH} \quad \text{OH} \quad \xrightarrow{\text{PCl}_3 \text{ Et}_3\text{N} \text{ toluene \(-20^\circ\text{C} \text{- reflux)}} \quad \text{HNRR'} \quad \xrightarrow{\text{Et}_3\text{N \text{ toluene \(-20^\circ\text{C} \text{- reflux)}}} \quad \text{O} \quad \text{O} \quad \text{P} \quad \text{N} \quad \text{R} \quad \text{R'} \quad (A)
\]

\[
\text{OH} \quad \text{OH} \quad \xrightarrow{\text{P(NMe}_2\text{)}_3 \text{ toluene \text{ reflux}}} \quad \text{O} \quad \text{P} \quad \text{N} \quad \text{Me} \quad \text{Me} \quad (B)
\]

Scheme 1. General synthesis routes for phosphoramidite ligands used in this study.
Fast Asymmetric Heck Reactions using Phosphoramidites

\[
\begin{align*}
\text{ligand} & \quad 2 & \quad 3 \\
R &= \quad \text{C}_2\text{H}_5 & \quad \text{CH}_3 \\
R' &= \quad \text{C}_2\text{H}_5 & \quad (\text{R})\cdot\text{CH}(\text{CH}_3)\text{Ph}
\end{align*}
\]

(R)-BINOL deriv.

\[
\begin{align*}
\text{ligand} & \quad 4 & \quad 5 & \quad 6 & \quad 7 & \quad 8 & \quad 9 \\
R &= \quad \text{CH}_3 & \quad \text{C}_2\text{H}_5 & \quad \text{CH}_3 & \quad \text{CH}_3 & \quad \text{CH}(\text{CH}_3)_2 & \quad \text{C}_2\text{H}_5 \\
R' &= \quad \text{CH}_3 & \quad \text{C}_2\text{H}_5 & \quad (\text{R})\cdot\text{CH}(\text{CH}_3)\text{Ph} & \quad (\text{S})\cdot\text{CH}(\text{CH}_3)\text{Ph} & \quad \text{CH}(\text{CH}_3)_2 & \quad \text{C}_2\text{H}_5 \\
\text{Ar} &= \quad 3.5\cdot(\text{CH}_3)_2\text{C}_6\text{H}_3 & \quad 3.5\cdot(\text{CH}_3)_2\text{C}_6\text{H}_3 & \quad 3.5\cdot(\text{CH}_3)_2\text{C}_6\text{H}_3 & \quad 3.5\cdot(\text{CH}_3)_2\text{C}_6\text{H}_3 & \quad \text{Ph} & \quad 2\cdot\text{Naphthyl}
\end{align*}
\]

(R,R)-TADDO deriv.  (S,S)-TADDO deriv.

Scheme 2. Overview of the bulky BINOL and TADDO type phosphoramidite ligands applied in these studies.

In solid state, the products formed appeared to be significantly less stable in solution and decomposition was observed in protic solvents and during column chromatography, even under basic conditions. Together with a very high solubility, this hampered purification of some of the ligands, especially for the bulky TADDO derivatives.

Ligand 14 was prepared in good yield via the reaction of (1R,2S)-\(\Lambda\)-benzylnorephedrine with an equimolar amount of 2,6-di(t-Bu)phenoxyPCL\(_2\) in a high-dilution experiment (Scheme 3).

4.2.2 Asymmetric Heck Reactions: Catalysis

4.2.2.1 Influence of the Backbone. As a model reaction we chose the intramolecular ring-closing reaction of cyclohex-1-ene carboxylic acid (2-iodophenyl)-methylamide (I) to the corresponding oxindole,\cite{25, 42} see Scheme 4. This reaction has been studied extensively\cite{43} and has great importance in constructing new chiral carbon centres in natural product syntheses. In this reaction the ring closure leads to the formation of two possible products: the 2-alkene (II) and the isomeric 3-alkene (III). The latter arises from reinsertion followed by $\beta$-H elimination of the 2-alkene product into the transient Pd-H bond (vide infra).

The catalytic active species were preformed in situ by stirring Pd(dba)$_2$ (2.5 mol\%) with 2-4 equiv. of the appropriate ligand at 50 °C in N,N-dimethylacetamide (DMA) for 15 minutes. After cooling to the desired reaction temperature N,N-diispropylethylamine (DIPEA) as the base (2-fold excess) and substrate were added and the reaction was monitored by TLC, GC, and $^1$H-NMR. Enantiomeric excesses were determined by chiral HPLC.

The results obtained using selected ligands are summarised in Table 1.
Fast Asymmetric Heck Reactions using Phosphoramidites

Table 1. Selected catalytic results obtained in the model reaction \( \text{I} \rightarrow \text{II} - \text{III} \) (Scheme 4) for several ligand backbones

<table>
<thead>
<tr>
<th>entry</th>
<th>Ligand 1</th>
<th>Temperature (°C)</th>
<th>Yield (%)</th>
<th>Ratio II : III ( % )</th>
<th>ee II (°) ( % ) ’ configuration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(R)-2</td>
<td>40</td>
<td>89</td>
<td>n.d.</td>
<td>&lt; 5 (S)</td>
</tr>
<tr>
<td>2</td>
<td>(R)-2</td>
<td>25</td>
<td>90</td>
<td>n.d.</td>
<td>&lt; 5 (S)</td>
</tr>
<tr>
<td>3</td>
<td>(R)-3</td>
<td>40</td>
<td>89</td>
<td>60 : 40</td>
<td>17 (S)</td>
</tr>
<tr>
<td>4</td>
<td>(R)-3</td>
<td>25</td>
<td>n.d.</td>
<td>59 : 41</td>
<td>20 (S)</td>
</tr>
<tr>
<td>5</td>
<td>14</td>
<td>40</td>
<td>92</td>
<td>56 : 44</td>
<td>17 (R)</td>
</tr>
<tr>
<td>6</td>
<td>(R,R)-5</td>
<td>40</td>
<td>99</td>
<td>50 : 50</td>
<td>38 (S)</td>
</tr>
<tr>
<td>7</td>
<td>(R,R)-5</td>
<td>25</td>
<td>97</td>
<td>42 : 58</td>
<td>48 (S)</td>
</tr>
</tbody>
</table>

* Experimental details: [Pd] = 2.5 mM Pd ligand substrate base = 1 : 2 : 40 : 80. Reaction time 2 h. determined by \(^1\)H NMR and or GC. determined by \(^1\)H NMR. determined by chiral HPLC (Chiralcel OD). not determined. absolute configuration determined by comparison with literature data, see ref. 44. For further information see experimental section.

As anticipated, the reaction rates are very high compared to the ‘classic’ diphosphine cases. For most ligands the reactions were completed within less than 15 minutes at 40 °C. When the reactions were run at room temperature, slightly longer reaction times were required (30-90 min.). These results show that a fast reaction induced by mono-ligated palladium complexes is feasible. Overman et al. already reported a large acceleration of the reaction rate using monodentate analogues of BINAP. The enantioselectivities obtained with these systems were low (19-27 °, ee). Application of phosphoramidites (R)-2, (R)-3 and 14 (entries 1-5) resulted in low ee’s of the product 2-alkene as well. However, major improvements could be made using TADDOL-based ligand (R,R)-5 as chiral auxiliary. In this case, the ee increased to 48 °. Therefore, we decided to focus our further research efforts on ligands based on this backbone.

4.2.2.2 Optimisation of Reaction Conditions. Solvent effects play an important role in Heck reactions. The best results are often obtained in polar media, such as acetonitrile or amides, which all have the ability to coordinate to the metal centre. The nature of the solvent applied has a large influence on the stereochemical outcome of the model reaction (see Table 2). The use of aprotic solvents resulted in slightly higher yields and much improved enantioselectivities. Toluene gave the best results, resulting in an ee of 56 ° under standard conditions in almost quantitative yield (see entry 7). Polar solvents might compete with the phosphoramidite ligands for coordination to the palladium centre, thus reducing the chiral induction. This competition is likely to be much smaller if not absent when non-coordinating solvents are used. From the point of stability, however, aprotic polar solvents can be preferable in cases where incomplete conversions are
Table 2. Solvent and temperature dependence in the model reaction $\text{I} \rightarrow \text{II} \cdot \text{III}$ using Pd ($R,R$)-5′

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Temperature (°C)</th>
<th>Yield (%)</th>
<th>Ratio II : III</th>
<th>ee II (%)</th>
<th>(S)-configuration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DMA</td>
<td>40</td>
<td>99</td>
<td>43 : 57</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>NMP</td>
<td>40</td>
<td>99</td>
<td>44 : 56</td>
<td>37</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>THF</td>
<td>40</td>
<td>99</td>
<td>38 : 62</td>
<td>46</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>MeCN</td>
<td>40</td>
<td>89</td>
<td>49 : 51</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>CH$_2$Cl$_2$</td>
<td>40</td>
<td>81</td>
<td>54 : 46</td>
<td>34</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>DMSO</td>
<td>40</td>
<td>n.d.</td>
<td>44 : 56</td>
<td>47</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Toluene</td>
<td>40</td>
<td>99</td>
<td>39 : 61</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Toluene</td>
<td>25</td>
<td>98</td>
<td>32 : 68</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Toluene</td>
<td>0</td>
<td>15</td>
<td>26 : 74</td>
<td>79</td>
<td></td>
</tr>
</tbody>
</table>

*Reaction conditions: see footnote Table 1.

obtained. For BINAP Pd catalysed cyclisations, polar solvents were shown to be beneficial for obtaining high ee’s, with N-methylpyrrolidine (NMP) giving the best results."

The enantioselectivity of the reaction showed a temperature dependence, i.e. higher ee’s were obtained at lower temperatures. Thus, upon lowering the reaction temperature to room temperature, the ee increased to 70°, when the reaction was carried out in toluene with DIPEA as the base (entry 8). Further decrease of the reaction temperature to 0 °C led to an even higher enantioselectivity of 79° ee (entry 9). In this case, however, a remarkable drop in the yield was observed, even using an increased palladium loading. The reason for this drop in turnover number is unclear at present.

Interestingly, the regioselectivity of the reaction towards the 2-alkene (X) seems to be inversely correlated to enantioselectivity observed in this product. This might indicate a mechanism of enantioselection in which a kinetic resolution plays a role (vide infra).

The influence of the nature of the catalyst precursor had little influence (Table 3). The application of Pd(OAc)$_2$ as the metal source (Table 3, entry 1, 2) gave smooth product formation in similar yield and enantioselectivity as the reaction using Pd(dba)$_2$. Variation of the number of equivalents of ligand (1.5-6 equiv. to Pd) did not influence the enantioselectivity within experimental error (entry 3-5), but the amount of ligand does affect the rate at which the Pd(0)(L*), species are being formed by exchange with the diene ligand(s) during the incubation period, as it takes less time for the reaction mixture to turn yellow during the incubation when more equivalents of ligand are used. In the case of incomplete coordination of the chiral ligand to Pd, the presence of achiral metal species might give rise to the competitive production of racemic product. However, the results obtained in our studies
Table 3. Variation of catalyst precursor and base in the model reaction $\text{I} \rightarrow \text{II} \rightarrow \text{III}$ using Pd (R,R)-5

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst precursor (R,R) to subs.</th>
<th>Base (equiv.)</th>
<th>Temperature (°C)</th>
<th>Yield (%)</th>
<th>Ratio II:III</th>
<th>ee II (%)</th>
<th>(S)-configuration</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Pd(OAc)$_2$ (3.0)</td>
<td>DIPEA</td>
<td>25</td>
<td>&gt; 99</td>
<td>35 65</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Pd(dba)$_2$ (2.0)</td>
<td>DIPEA</td>
<td>25</td>
<td>98</td>
<td>32 68</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Pd(dba)$_2$ (1.5)</td>
<td>DIPEA</td>
<td>40</td>
<td>n.d.</td>
<td>41 59</td>
<td>53</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Pd(dba)$_2$ (3.0)</td>
<td>DIPEA</td>
<td>40</td>
<td>&gt; 99</td>
<td>39 61</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Pd(dba)$_2$ (6.0)</td>
<td>DIPEA</td>
<td>40</td>
<td>n.d.</td>
<td>41 59</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>Pd(dba)$_2$ (2.0)</td>
<td>DIPEA</td>
<td>40</td>
<td>&gt; 90</td>
<td>43 57</td>
<td>38</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Pd(dba)$_2$ (2.0)</td>
<td>Et$_3$N</td>
<td>40</td>
<td>&gt; 90</td>
<td>41 59</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Pd(dba)$_2$ (3.0)</td>
<td>Proton</td>
<td>25</td>
<td>94</td>
<td>40 60</td>
<td>66</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Pd(dba)$_2$ (2.0)</td>
<td>KOAc</td>
<td>25</td>
<td>&lt; 5</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Pd(dba)$_2$ (3.0)</td>
<td>Ag$_2$PO$_4$</td>
<td>25</td>
<td>n.d.</td>
<td>46 54</td>
<td>43</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>Pd(dba)$_2$ (2.0)</td>
<td>DIPEA</td>
<td>25</td>
<td>35</td>
<td>33 67</td>
<td>70</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Pd(dba)$_2$ (2.0)</td>
<td>DIPEA</td>
<td>25</td>
<td>75</td>
<td>33 67</td>
<td>69</td>
<td></td>
</tr>
</tbody>
</table>

" Reaction conditions: see footnote Table 1. "*" Reaction carried out in DMA. "**1.8-bis(dimethylamino)naphthalene."**1.0 equiv. of KF added. "*"1.0 mol% Pd applied

The nature of the base applied was also tested. Tertiary amines, e.g. triethylamine or DIPEA, gave very similar results (entries 6 and 7). The use of "proton sponge" (1.8-bis(dimethylamino)naphthalene) as a strong organic base did not lead to a significant change in enantioselectivity either. The presence of Ag$_2$PO$_4$, often successfully applied as halide-scavenger and base in the case of Pd(diphosphine) asymmetric Heck catalysis, resulted in low yield and low ee (entry 9). Possibly, the capture of the halide (I) ligand by the silver cation leaves the metal centre, already being a coordinatively unsaturated species, in a highly unstable state, resulting in rapid decomposition to palladium metal. The formation of palladium metal was indeed observed in this case, as opposed to other reactions. Other inorganic bases, e.g. KOAc gave hardly any reaction under these conditions, in accordance with the results in Chapter 3.
4.2.2.3 Ligand Variation. As already stated above, the class of ligands presented in this study is extremely suitable for a modular approach, enabling extensive ligand modification at different positions in the molecule. For the TADDOL-based ligands this is possible through variation of 1) the aryl substituents in the backbone, 2) the type of substituents introduced through the acetal formation at the five-membered ring, and 3) the amine moiety.

Table 4. Ligand variation in the model reaction I $\rightarrow$ II $\rightarrow$ III$^\text{a,b}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Yield (%)</th>
<th>Ratio II : III</th>
<th>ee II (%)</th>
<th>ee III (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(R,R)-8</td>
<td>n.d.</td>
<td>39.61</td>
<td>&lt; 5 (S)</td>
<td>n.d.</td>
</tr>
<tr>
<td>2</td>
<td>(R,R)-9</td>
<td>n.d.</td>
<td>26.74</td>
<td>44 (S)</td>
<td>7 (-)</td>
</tr>
<tr>
<td>3</td>
<td>(R,R)-12</td>
<td>61</td>
<td>31.69</td>
<td>68 (S)</td>
<td>19 (-)</td>
</tr>
<tr>
<td>4</td>
<td>(R,R)-4</td>
<td>89</td>
<td>24.76</td>
<td>45 (S)</td>
<td>15 (-)</td>
</tr>
<tr>
<td>5</td>
<td>(R,R)-5</td>
<td>98</td>
<td>32.68</td>
<td>70 (S)</td>
<td>15 (-)</td>
</tr>
<tr>
<td>6</td>
<td>(S,S)-6</td>
<td>&gt; 99</td>
<td>32.68</td>
<td>69 (R)</td>
<td>16 (-)</td>
</tr>
<tr>
<td>7</td>
<td>(R,R,R)-6</td>
<td>&gt; 99</td>
<td>48.52</td>
<td>40 (S)</td>
<td>21 (-)</td>
</tr>
<tr>
<td>8</td>
<td>(R,R,S)-7</td>
<td>&gt; 99</td>
<td>44.56</td>
<td>51 (S)</td>
<td>24 (+)</td>
</tr>
<tr>
<td>9</td>
<td>(S,S,R)-6</td>
<td>&gt; 99</td>
<td>28.72</td>
<td>57 (R)</td>
<td>27 (-)</td>
</tr>
<tr>
<td>10</td>
<td>(S,S,S)-7</td>
<td>&gt; 99</td>
<td>55.45</td>
<td>39 (R)</td>
<td>18 (-)</td>
</tr>
<tr>
<td>11</td>
<td>(R,R)-11</td>
<td>91</td>
<td>23.77</td>
<td>46 (S)</td>
<td>16 (-)</td>
</tr>
<tr>
<td>12</td>
<td>(R,R)-10</td>
<td>84</td>
<td>22.78</td>
<td>43 (S)</td>
<td>20 (-)</td>
</tr>
<tr>
<td>13</td>
<td>(R,R)-13</td>
<td>&gt; 99</td>
<td>26.74</td>
<td>8 (R)</td>
<td>7 (+)</td>
</tr>
</tbody>
</table>

$^a$ Reaction conditions: see footnote Table 1. $^b$ Absolute stereochemical configuration was not determined. 4.0 equivalents (to Pd) of ligand applied.

The results for the different ligands in the model Heck reaction are shown in Table 4. The observed ee’s are very sensitive to modification of the aryl substituents in the TADDOL backbone. Thus, ligands 9 and 8, with 2-naphthyl and phenyl substituents respectively, give product 11 in low ee (44 \(\%\) and <5 \(\%\) resp.), whereas ligand 5 results in 70\% ee under the same conditions. Furthermore, replacement of the two methyl substituents at the dioxalan system by a cyclohexyl group (ligand 11) does slightly decrease enantioselectivity (entry 3). This can be explained by the fact that the cyclohexyl moiety, being sterically more restricted, introduces slightly different ring tension in the backbone and therefore results in different chiral induction. Finally, variation of the amine moiety results in a sharp optimum for the diethylamino substituent. Lower ee’s are obtained using ligands with the smaller dimethylamino- (entry 4) or larger N,N-dimethylbenzylamine moiety (entries 7-10). We have been unable to isolate corresponding ligands with even larger substituents on nitrogen (e.g. isopropyl groups). When ligand (S,S)-5 is used,
having the opposite chirality in the TADDOLate backbone, the same regio- and stereoselectivities are observed, with the opposite enantiomers formed in excess, as can be seen from entries 5 and 6 in Table 3.

Interesting results are obtained from the application of ligands with the chiral \( \alpha \)-dimethylbenzylamine moiety in the reaction. In this case, a chiral cooperativity between the chirality of the TADDOLate and of the amine is possible, giving information on the important factors steering the enantioselectivity of the reaction. From entries 7-10 it can be concluded that the stereochemical outcome of the ring closure to \( \text{II} \) is mainly determined by the TADDOLate backbone structure of the ligands, as indicated by the small influence of the configuration of the amine-carbon on the enantiomer of \( \text{II} \) formed. Thus, on changing the configuration in the amine moiety, going from ligand \((S,S,R)-6 \) to \((S,S,S)-7 \), a slight drop in enantioselectivity from 57\% \( \text{ee} \) to 39 \% \( \text{ee} \) in \((R)-\text{II} \) is observed (entries 9 and 10). At the same time, the ee in product \( \text{III} \) changes from 27 \% \( \text{ee} \) to 18 \% \( \text{ee} \) of the opposite enantiomer! This remarkable change is accompanied by a large shift of the regioselectivity from approximately 28 \% \( \text{ee} \) \( \text{II} \) to over 50 \% \( \text{ee} \).

Application of phosphoramidite ligands possessing a potentially coordinating heteroatom (oxygen in the case of \( \text{II} \), nitrogen in \( \text{I0} \)) results in lower enantioselectivity compared to \( \text{S} \). Apparently, the second donor atom does play a role in modifying the catalyst properties and therefore the catalytic results, but not in a beneficial way. Phosphite-derivative \( \text{I3} \) showed low stereoselectivity, although the reaction rate observed was even higher than that found for the phosphoramidite ligands.

4.2.3 Origin of Enantioselectivity: Mechanistic Aspects

4.2.3.1 Nature of the Catalytically Active Species. As already indicated above, several observations indicate that our working hypothesis, i.e. the catalytically active species consists of a Pd species with only one bulky ligand coordinated, is valid under the conditions used. The reaction rates obtained in our model reaction are several orders of magnitude higher than observed by Feringa in his intramolecular asymmetric Heck reaction.\(^{[35]}\) This large difference can be explained by the fact that the ligands employed in their studies are not sufficiently bulky to enforce mono-coordination. If ligation of \( \omega \omega \) phosphoramidites occurs, this probably leads to a slower oxidative addition and insertion, mainly caused by steric factors. If one of these steps becomes rate determining, in going from mono-coordination to bis-coordination, this can lead to overall retardation of the ring closure reaction. (Additionally, it should be noted that the influence of the difference in substrate cannot be ruled out as a cause for the large rate difference). The enantioselectivity of the reaction is not sensitive to the number of equivalents of ligand employed, going from 1.5 to 6 equivalents. If the ee's observed are a resultant of different, for example.
Figure 2. Dependence of the enantioselectivity of II using mixtures of ligand 5 of different enantiopurity, showing a linear correlation. Experimental conditions as in Table 3, entry 11.

Pd(L*) and Pd(L*)₂, species both showing activity and existing as dynamic equilibria, the enantioselectivity would be expected to be dependent on the Pd/L ratio (assuming different enantioselectivities for the different species). Even if bis-coordinated species are present that are not reactive, the number of equivalents of ligand employed should have a large effect on the rate of the reaction, which is not observed.

To test whether the actual catalyst is mono-coordinated under catalytic conditions, we decided to investigate the dependence of the enantioselectivity of the reaction on the enantiopurity of the ligand. In general, such a correlation can give valuable information on the exact nature of the catalytically active species in asymmetric catalysis, as shown in kinetic models by Blackmond and Kagan. The results obtained under standard conditions using ligand (R,R)-5 are depicted in Figure 2. From this it can be concluded that, within experimental error, a linear correlation exists between the ee of the 2-alkene product (II) and the ee of the ligand. The absence of a non-linear

\[
\text{Scheme 5. Synthesis of [Pd(R,R)-5(4-CNC,H)(μ-Br)]₂.}
\]
effect (NLE) is in agreement with a stereoselectivity determining step in which only one chiral unit is coordinated to the metal centre, but it does not rule out a system containing catalytically active Pd(L*)₂ species in which the NLE is accidentally zero.⁴⁷

4.2.3.2 Complex Synthesis and Structure. To gain further insight in the palladium species involved in the reaction, we synthesised complex [Pd((R,R)-5)(4-CN,C₆H₄)(μ-Br)]₂ which is a putative intermediate complex formed after oxidative addition of an aryl halide to a Pd(0) precursor. Thus, reaction of 4-bromobenzonitrile to a mixture of Pd(dba)₂ and 4 equivalents of ligand (R,R)-5 in toluene at room temperature afforded the Pd(II)-complex in reasonable yield (Scheme 5). In ³¹P NMR, the complex showed a single resonance at 92.7 ppm (CDCl₃), indicating formation of either a trans complex of formula Pd(L*)₂(Ar)(Br) or a dimeric complex of type [Pd(L*)(Ar)(Br)]₂. From integration in ¹H NMR we concluded that the dimeric form is the actual structure formed.

We were able to grow crystals suitable for X-ray analysis. As is depicted in Figure 3, the compound indeed has a dimeric structure, with only one phosphoramidite coordinated to the metal centre. The dimer has approximately square planar geometry around Pd, with slightly larger angles between the phosphorus and neighbouring ligands (∠(P(3)-Pd(1)-Br(2)) = 93.76(2)° and ∠(C(52)-

![Figure 3](image_url). Crystal structure of cis-[Pd((R,R)-5)(4-CN,C₆H₄)(μ-Br)]₂. Hydrogen atoms are omitted for clarity.
Pd(1)-P(3) = 93.06(9)°, and consequently smaller L-Pd-Br angles (e.g. 86.72(8)° for \( \angle(C(52)\)-Pd(1)-Br(1))\), see Table 5) than the optimal 90°. This small distortion is likely to be caused by the large steric bulk of the phosphoramidite ligand. The halide anions function as bridging ligands, resulting in a Pd(1)-Br(1) distance of 2.5082(4) Å (trans relationship to P) and 2.5455(4) Å (Pd(1)-Br(2); cis). The plane of the 4-cyanophenyl ligand is not perpendicular to the coordination plane, but is tilted towards the less crowded side of the complex (\( \angle(P(3)\)-Pd(1)-C(52)-C(53) = -78.3(3)°). The phosphoramidite ligands adopt a cis configuration, giving the dinuclear complex C₃-symmetry with the symmetry axis formed by the two bromide ligands. The compound is likely to exist in both cis and trans isomers in solution, as was observed by low temperature NMR in the case of non-chiral Pd(phosphoramidite)(Ar)(Br)-dimers (see Chapter 3 of this thesis). Crystal packing factors might be responsible for the preferred cis geometry in the solid state. The results we have obtained from earlier kinetic studies using an achiral analogue\(^{36}\) proved that a rapid equilibrium is present between the dimeric and the monomeric form of the complexes, with the equilibrium strongly shifted to the inactive dimeric form (the only species observed using different spectroscopic techniques). Assuming that the chiral species behave similarly, this dimer represents the resting state of the chiral catalyst. To the best of our knowledge, this X-ray analysis represents the first example of a (phosphoramidite)Pd(organyl)halide crystal structure reported (recently, X-ray characterisation of a dimeric Pd(benzyl)(Br)(bulky phosphite) complex was reported by Ziolkowski\(^{48}\)).

Figure 4. Top-view (perpendicular to the P-Pd-Br plane) of cis-[Pd((R,R)-5)(4-CNC₅H₅)(\(\mu\)-Br)]₂ (only half of the dimer is shown for clarity).
The TADDOL backbone moieties show a near-\( C_2 \) type symmetric conformation, as is often the case in complexes where the TADDOLate functions as the ligand itself (e.g. Ti(TADDOLate)\( C_2 \) complexes). The \( P(3)-O(9) \) bond is virtually in the coordination plane, \( \angle (C(52)-Pd(1)-P(3)-O(9)) \) being \( 8.13(11)° \). This propeller-like conformation is often regarded as an important condition for inducing high enantioselectivities in asymmetric transformations using transition metal complexes. The ligand as a whole and the monomeric form of the corresponding Pd complexes show \( C_2 \) symmetry. The \( C_2 \) symmetry of the TADDOLate backbone is not fully translated to the environment of the Pd centre, because of incomplete ‘embracing’ of the metal by the ligand. Therefore, the exact mechanism of chiral induction in this asymmetric Heck reactions from the ligand to the substrate remains difficult to understand.

**Table 5.** Selected bond lengths and angles of \( cis-[Pd(R,R)-5][4-CNC,H_3](\mu-Br)_2] \)

<table>
<thead>
<tr>
<th>Bond length (Å)</th>
<th>Bond length (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pd(1)-Br(1)</td>
<td>2.5082(4)</td>
</tr>
<tr>
<td>Pd(1)-Br(2)</td>
<td>2.5455(4)</td>
</tr>
<tr>
<td>Pd(1)-P(3)</td>
<td>2.2232(7)</td>
</tr>
<tr>
<td>Pd(1)-C(52)</td>
<td>2.002(3)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bond length (Å)</th>
<th>Bond length (Å)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P(3)-O(9)</td>
<td>1.607(2)</td>
</tr>
<tr>
<td>P(3)-O(51)</td>
<td>1.601(2)</td>
</tr>
<tr>
<td>P(3)-N(4)</td>
<td>1.632(3)</td>
</tr>
<tr>
<td>N(57)-C(56)</td>
<td>1.144(6)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Bond/dihedral angle (°)</th>
<th>Bond/dihedral angle (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Br(1)-Pd(1)-P(3)</td>
<td>175.32(2)</td>
</tr>
<tr>
<td>Br(2)-Pd(1)-C(52)</td>
<td>172.96(8)</td>
</tr>
<tr>
<td>Br(1)-Pd(1)-C(52)</td>
<td>86.72(8)</td>
</tr>
<tr>
<td>Br(2)-Pd(1)-P(3)</td>
<td>93.76(2)</td>
</tr>
<tr>
<td>Pt(3)-Pd(1)-C(52)</td>
<td>93.06(9)</td>
</tr>
<tr>
<td>Pd(1)-Br(1)-Pd(1)( ^{a} )</td>
<td>94.28(1)</td>
</tr>
<tr>
<td>Pd(1)-Br(2)-Pd(1)( ^{a} )</td>
<td>92.49(1)</td>
</tr>
<tr>
<td>Br(2)-Pd(1)-Br(1)( ^{a} )</td>
<td>0.00(4)</td>
</tr>
<tr>
<td>Pd(1)( ^{a} )</td>
<td></td>
</tr>
<tr>
<td>C(52)-Pd(1)-Br(1)( ^{a} )</td>
<td>-177.74(8)</td>
</tr>
<tr>
<td>Pd(1)( ^{a} )</td>
<td>-175.33(2)</td>
</tr>
<tr>
<td>P(3)-Pd(1)-P(3)-O(9)</td>
<td>170.16(8)</td>
</tr>
<tr>
<td>C(52)-Pd(1)-P(3)-O(9)</td>
<td></td>
</tr>
</tbody>
</table>

**4.2.3.3 Kinetic Resolution Mechanism.** A complicating factor in the reaction studied here is the possibility of isomerisation of the product alkenes (II and III), as illustrated by the mechanism
Scheme 6. Mechanism of isomerisation of initially formed II to III, leading to racemisation.

In Scheme 6. In this mechanism the Pd-alkyl complex formed after initial oxidative addition and insertion of the alkene part of the substrate in the Pd-aryl bond undergoes β-H elimination. The resulting Pd-alkene complex may undergo two reactions: either dissociation of the product 2-alkene takes place or reinsertion of the alkene into the Pd-H bond. If reinsertion takes place with Pd-C bond formation at the carbon atom one further down the ring of the cyclohexenyl moiety, a new Pd-alkyl species is formed. β-H elimination from this species can also give the 3-alkene product complex, which again can reinsert or dissociate. In this way, the palladium centre could 'run' down the whole cyclohexenyl ring if alkene dissociation at all stages is much slower than formation of the Pd-alkyl species via insertion. This is important to notice, since the two pairs of 2-alkene (II) and 3-alkene (III) product are in fact pairs of opposite enantiomers! This means that rapid equilibration of the product isomers could lead to racemisation.

In the present case the observed selectivity towards the 2-alkene appears to be inversely correlated to the enantioselectivity of the reaction (see Table 3), indicating that an unspecific isomerisation / racemisation mechanism as described above is not operative. More likely, a kinetic resolution mechanism applies. In such a kinetic resolution mechanism, the formation of the Pd-(II) complex initially takes place with a certain (low) enantiodiscrimination. The chiral environment around the metal centre, however, causes one of the diastereomeric complexes formed to mainly follow the dissociation pathway, giving II in higher ee, while the other diastereomer preferentially reinserts and thereby isomerises to a Pd-(III) complex. The fact that the observed enantioselectivity in III in all cases is much lower than that in the corresponding II, and also in some cases differs in the enantiomer of III formed in excess (while the same enantiomer in II is formed as major product) indicates that the β-H elimination-reinsertion is faster for the III-product than for alkene II. Similar kinetic resolution mechanisms were already proposed by Hayashi and coworkers in the case of Pd(diphosphine) catalysed asymmetric intermolecular Heck reactions, and also by Overman in intramolecular asymmetric Heck cyclisations.

To obtain more evidence for our hypothesis, we tested substrate IV in the asymmetric Heck reaction, which cannot undergo isomerisation. Under the same conditions applied to I (Scheme 7),
Scheme 7. Asymmetric Heck cyclisation of IV to V without possible isomerisation.

this resulted in formation of the product (V) in 27 % ee, albeit in low yield (possibly caused by electronic or steric deactivation of the double bond). The fact that in this case the observed enantioselectivity is much lower supports our view that most likely the ee obtained for II is largely due to a kinetic resolution process.

4.3 Conclusions

To conclude, we have shown that bulky, chiral monodentate phosphoramidite ligands give rise to very rapid asymmetric intramolecular Heck reactions of aryl iodides I and IV under extremely mild conditions (room temperature or even lower). This demonstrates the viability of the concept of combining enhanced reaction rates with inducing enantioselectivity by the use of bulky, electron-poor monodentate ligands, which give mono-ligand metal complexes. The corresponding palladium complexes exist as dimers, which are the resting state of the catalyst during the reaction. The observed enantioselectivity is likely to originate from a kinetic resolution mechanism.

Although we have expanded the toolbox with a variety of ligands, we have not been able to elucidate the exact origin of the asymmetric induction in the initial carbon-carbon bond forming step using X-ray data or three-dimensional modelling. The same applies to the subsequent stereoselective isomerisation steps. For example, the large differences observed in the application of phosphoramidites that differ only slightly in structural properties remain puzzling so far and require further research. Also, it is unclear whether the insertion step of the alkene into the Pd-aryl bond takes place in a neutral, four-coordinated complex, or whether ligand dissociation (e.g. the halide anion) has to occur first.

The successful application of chiral monodentate ligand systems as in our studies presented here in addition to the known bidentate diphosphines or P-N ligands, has even further enlarged the number of possible mechanistic pathways to be considered. Obtaining further knowledge of the details determining the exact stereochemical outcome of C-C bond forming reactions therefore will remain an enormous challenge.
4.4 Experimental Section

**General remarks.** All experiments were carried out under a purified nitrogen atmosphere using standard Schlenk techniques unless otherwise noted. Solvents were purchased from Acros and dried prior to use. Toluene was distilled from sodium; THF, hexanes and diethyl ether from sodium benzophenone ketyl and dichloromethane from calciumhydride. All amines employed were distilled from calciumhydride prior to use. Phosphortrichloride was distilled prior to use and stored at 20 °C. HMP T and 1.8-bis(dimethylamino)naphthalene were used as received from Aldrich.

\(^1\)H NMR spectra were recorded on a Varian Mercury 300 (300.1 MHz) in CDCl\(_3\), and are reported in ppm using tetramethylsilane (\(\text{H} \text{and} \text{^13C}\)) or H\(_3\)PO\(_4\) (\(^1\)P) as external standard. Data are reported as follows: (b = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet; integration; coupling constant(s) in Hz; assignment). \(^1\)C NMR spectra were recorded in proton decoupled mode. Thin-layer chromatography was carried out using Macherey-Nagel SIL G UV plates of Kieselgel 60. TLC plates for the use with the ligands was neutralised first by doping with triethylamine. Column chromatography was performed using silica 60 (SDS Chromagel, 70-200 μm). GC measurements were performed on a Shimadzu GC-17A apparatus (split/splitless, equipped with a F.I.D. detector and a BPX35 column (internal diameter of 0.22 mm, film thickness 0.25 μm, carrier gas 70 kPa He)) or on an Interscience HR GC Mega 2 apparatus (J&W Scientific, DB-1 column, 30 m; film 3.0 μm carrier gas 70 kPa He, F.I.D. detector). GC MS measurements (E.I. detection) were performed on a HP 5890 5971 apparatus, equipped with a ZB-5 column (5% cross-linked phenyl polysiloxane) with an internal diameter of 0.25 mm and film thickness of 0.25 μm. Melting points were measured on a Gallenkamp melting point apparatus and are uncorrected. HPLC measurements for determination of enantiomeric excesses were performed using a Gilson apparatus equipped with a Dynamax UV-1 absorbance detector. High Resolution Mass Spectra were recorded at the Department of Mass Spectroscopy at the University of Amsterdam using FAB ionisation on a J-1OL JMS SX SX102A four sector mass spectrometer with 3-nitrobenzyl alcohol as a matrix. Elemental analyses were performed at the Department of Microanalysis at the Rijksuniversiteit Groningen, The Netherlands.

The TADDOL-type backbones employed were synthesised according to literature procedures.\(^{[51-52]}\) (R)-3,3'-trimethylsilyl-1,1'-binaphthyl-2,2'-diol was synthesised as reported by Buisman et al.\(^{[53]}\) cyclohex-1-ene-carboxylic acid (2-iodophenyl)-methyl-amide\(^{[41]}\) and 1,4-dioxaspiro[4.5]dec-7-ene-8-carboxylic acid (2-iodophenyl)-methyl-amide\(^{[41]}\) were prepared as reported. N-Benzyl-(1R,2S)-norephedrine was synthesised by a literature procedure.\(^{[41]}\)
Ligand Synthesis

3-benzyl-2-(2,6-di-tert-butylphenoxy)-4-(S)-methyl-5-(R)-phenyl-1,3,2-oxazaphospholidine (14): N-benzyl-(1R,2S)-norephedrine (340 mg, 1.40 mmol) was dissolved in 40 mL of dry toluene. Separately, 2,6-di(tert-butyl)phenoxyphosphordichloridite (433 mg, 1.40 mmol) was dissolved in 40 mL of dry toluene. Both solutions were slowly dropwise added, simultaneously, to a solution of 3 mL triethylamine in 40 mL of toluene at -40 °C. Care was taken to ensure that the rate of addition of both reactant-containing solutions was as equal as possible. After complete addition, the resulting reaction mixture was warmed to room temperature and stirred for 48 hours. The formed ammonium salts were filtered and the solvent removed in vacuo. This resulted in a slightly yellow powder as the crude product. Pure compound was obtained by crystallisation from diethyl ether, followed by washing of the formed crystals with cold diethyl ether (5 mL) and acetonitrile (2 × 5 mL). Yield: 365 mg (55%).

¹H NMR: δ = 7.38-7.34 (m, 12H, Ar-H). 6.99 (t, 1H, J = 7.7 Hz, Ar-H). 5.13 (d, 1H, J = 6.0 Hz, CH(Ph)O). 4.60 (dd, 1H, J = 15.1, 7.9 Hz). 4.09 (dd, 1H, J = 23.2, 7.9 Hz). 3.31 (m, 1H, CH(Me)N). 1.61 (s, 18H, (CH₃)₃). 1.00 (d, 3H, J = 6.8 Hz); ¹³C (APT) NMR: δ = 152.1 (d, J = 11.0 Hz), 143.7, 139.3, 138.2, 128.9, 128.3, 128.1, 128.1, 127.9, 126.7, 126.3, 122.7, 86.0 (d, J = 12.2 Hz). 55.2, 51.0 (d, J = 30.5 Hz). 35.8, 32.4, 15.6; ³¹P NMR: δ = 154.9, HRMS: calc. for C₃₀H₃₀NO₅P: m/z 476.2718, found: 476.2746. Anal. calc. for C₃₀H₃₀NO₅P: C, 75.76, H 8.05, N 2.95% found: C, 75.58, H 8.07, N 3.06%.

(R)-O,O′-(1.1′)-Dinaphthyl-2,2′-diyl-3,3′-di(trimethylsilyl)-phosphorimidit e: (R)-3,3′-trimethylsilyl-1,1′-binaphthyl-2,2′-diol (1.00 g, 2.31 mmol) was azeotropically dried by dissolving it in 10 mL of dry toluene followed by evaporation in vacuo of the solvent (2 times). The dry starting material was then dissolved in 25 mL toluene. 242 µL PCl₃ (381 mg, 2.77 mmol) and 1.3 mL triethylamine (0.93 g, 9.2 mmol) were dissolved in 50 mL toluene and at 0 °C added dropwise to the diol solution. After stirring overnight, the resulting suspension was stirred at 50 °C for 1 hour. After cooling to room temperature, the suspension was filtered and the solvent evaporated to give a yellow, air-sensitive powder (³¹P; ¹H NMR: δ = 176 ppm). This compound was not characterised further, but used immediately in further reactions.

O,O′-(1.1′)-Dinaphthyl-2,2′-diyl-3,3′-di(trimethylsilyl)-N,N-diethylphosphorimidite ([(R)-2]: (R)-O,O′-(1.1′)-Dinaphthyl-2,2′-diyl-3,3′-di(trimethylsilyl)-phosphorimidite (546 mg, 1.10 mmol) was dissolved in 25 mL toluene and cooled to 0 °C and triethylamine (0.23 mL, 1.65 mmol) was added. Next, a solution of diethylamine (0.17 mL, 1.65 mmol) in 20 mL toluene was added dropwise. After complete addition, the solution was warmed to room temperature and stirred for 2
hours. Subsequently the cloudy mixture was stirred overnight at 75 °C. After cooling to room temperature the resulting suspension was filtered and all volatiles evaporated in vacuo. The crude product was washed with hexanes (2 x 15 mL) and purified by column chromatography (SiO₂ eluents EtOAc Et₂N PE = 5:5:90) to afford the product as a white powder. Yield: 110 mg (19%). Precipitation from the hexane washing fractions yielded another 100 mg pure product.

¹H NMR: δ = 8.04 (d, 2H, J = 12.3 Hz, Ar-H), 7.89 (d, 2H, J = 8.1 Hz, Ar-H), 7.39-7.05 (m, 6H, Ar-H), 2.94 (t, 4H, NCH₂CH₂), 1.02 (t, 6H, NCH₂C₂H₅), 0.47 (s, 9H, Si(CH₃)₃); ¹³C¹H NMR: δ = 154.1, 154.0, 137.0, 136.8, 134.3, 134.1, 132.9, 132.5, 131.0, 130.2, 128.5, 128.4, 127.1, 127.0, 126.4, 126.3, 124.6, 124.3, 122.9, 122.8, 121.3, 40.6 (m), 29.9, 15.7, 0.3, 0.2; ³¹P³H NMR: δ = 150.2; HRMS (M-H⁻): calc. for C₃₆H₃₆NO₂PSi₂: m/z 532.2257, found: 532.2274. Anal. calc. for C₃₆H₃₆NO₂PSi₂: C. 67.76, H 7.20, N 2.63; found: C. 67.47, H 7.42, N 2.67.

O.O'-[1,1'-Dinaphthyl-2,2'-diyl-3,3'-di(trimethylsilyl)]-N-methyl-V-(R)-1-phenylethylphosphoramidite ((R)-3): This compound was prepared analogously to (R)-2 from (R)-O.O'-[1,1'-Dinaphthyl-2,2'-diyl-3,3'-di(trimethylsilyl)]-phosphorochloridite (546 mg, 1.10 mmol) and (R)-(-)-N,α-dimethylbenzylamine (0.22 g, 1.65 mmol). Purified by column chromatography (SiO₂ eluents EtOAc/Et₂N PE = 2.5:5:92.5). Yield: 251 mg (38%) of a white powder.

¹H NMR: δ = 8.06 (d, 2H, J = 4.8 Hz, Ar-H), 7.88 (dd, 2H, J = 8.3, 1.1 Hz, Ar-H), 7.46-7.01 (m, 11H, Ar-H), 4.90 (m, 1H, NCH₂(Me)(Ph)), 2.13 (d, 3H, J = 4.3 Hz, NCH₃), 1.63 (d, 3H, J = 7.0 Hz, NCH₂(CH₃)), 0.44 (s, 9H, Si(CH₃)₃), 0.36 (s, 9H, Si(CH₃)₃); ¹³C¹H NMR: δ = 153.5 (t, J = 1.5 Hz), 142.0, 136.7, 16.6, 133.9, 133.7, 132.3, 131.9, 130.5, 129.8, 128.0, 127.8, 127.4, 126.8, 126.7, 126.5, 126.0, 124.2, 124.1, 122.5, 122.5, 121.1, 121.1, 56.1, 55.5, 45.3, 29.5, 27.5, 19.1, 19.0, 0.3, 0.2, 0.2; ³¹P³H NMR: δ = 145.6; HRMS (M-H⁻): calc. for C₃₆H₃₆NO₂PSi₂: m/z 594.2414, found: 594.2415. Anal. calc. for C₃₆H₃₆NO₂PSi₂: C. 70.79, H 6.79, N 2.36; found: C. 70.49, H 7.04, N 2.45.

(1,7R)-4-Dimethylamino-9,9-dimethyl-2,2,6,6-tetra(3,5-dimethylphenyl)-3,5,8,10-tetraoxa-4-phosphabicyclo[5.3.0]decane, ((R,R)-4): (2R,3R)-O-isoproplidene-1,1,4,4-tetra(3,5-dimethylphenyl)-threitol (300 mg, 0.52 mmol) was dried by repeatedly (3 times) dissolving the compound in 5 ml of toluene and evaporating thoroughly to dryness. Next, the diol was dissolved in 20 ml of toluene. The solution was cooled to 0 °C, and a solution of hexamethyl phosphoramide (HMPT) (113 µl, 0.62 mmol) together with approx. 1 mg of 1H-tetrazole in 5 ml of toluene was added dropwise. The mixture was warmed to room temperature and stirred for 2 hrs. and subsequently refluxed for 24 hrs. After removal of the solvent in vacuo the resulting foamy solid
was purified by column chromatography (hexanes EtOAc triethylamine, 95:5:2.5:5:1:1) to yield the product as a white powder. Yield: 165 mg (49%).

\[ \text{NMR: } \delta = 7.39 (s, 2H, Ar-H), 7.19 (s, 2H, Ar-H), 7.06 (s, 4H, Ar-H), 6.87 (s, 2H (partial overlap), Ar-H), 6.86 (s, 2H (partial overlap), Ar-H) 5.08 (double d, 1H, J = 3.3, 8.2 Hz, CH), 4.77 (d, 1H, J = 8.2 Hz, CH), 2.73 (d, 6H, J = 10.4 Hz, NCH$_3$)$_3$, 2.29-2.26 (m, 24H, ArCH$_2$), 1.35 (s, 3H, OCCH$_3$), 0.28 (s, 3H, OCCH$_2$); \text{NMR: } \delta = 147.2, 146.9, 142.0, 137.4, 137.0, 136.7, 136.4, 129.3, 129.0, 128.8, 127.1, 126.8, 126.7, 125.3, 125.1, 111.8, 83.2, 83.0, 82.7, 81.8, 81.3, 81.2 (the area 83.2-81.2 ppm contains some extra resonances probably due to P-C coupling.)

35.5 (d, J$_{PC} = 19.5$ Hz), 27.9, 25.7, 21.9, 21.8; \text{P; H; NMR: } \delta = 139.7. \text{HRMS (M-H$^-$): calc. for C$_{41}$H$_{51}$N$_0$P: m/z 652.3556, found: 652.3557; Anal. calc. for C$_{41}$H$_{51}$N$_0$P: C, 75.55, H 7.73, N 2.15; found: C, 75.17, H 7.84, N 2.19.

(1S,7S)-4-Dimethylamino-9,9-dimethyl-2,2,6,6-tetra(3,5-dimethylphenyl)-3,5,8,10-tetraoxa-4-phosphabicyclo[5.3.0]decane, ((S,S)-4): This compound was prepared as described ($R$,R)-4 from 25,35-O-isopropylidene-1,1,4,4-tetra(3,5-dimethylphenyl)threitol (500 mg, 0.86 mmol) and HMP T (188 ml, 1.03 mmol). Yield: 310 mg (55%).

\[ \text{NMR: } \delta = 7.44 (s, 2H, Ar-H), 7.24 (s, 2H, Ar-H), 7.11 (s, 4H, Ar-H), 6.91 (s, 3H (partial overlap), Ar-H), 6.88 (s, 1H (partial overlap), Ar-H) 5.12 (double d, 1H, J = 3.3, 8.2 Hz, CH), 4.81 (d, 1H, J = 8.2 Hz, CH), 2.78 (d, 6H, J = 10.5 Hz, N(CH$_3$)$_3$), 2.33-2.30 (m, 24H, ArCH$_2$), 1.40 (s, 3H, OCCH$_3$), 0.33 (s, 3H, OCCH$_2$); \text{NMR: } \delta = 139.7. \text{HRMS (M-H$^-$): calc. for C$_{41}$H$_{51}$N$_0$P: m/z 652.3556, found: 652.3533; Anal. calc. for C$_{41}$H$_{51}$N$_0$P: C, 75.55, H 7.73, N 2.15; found: C, 75.62, H 7.92, N 2.21.

(1R,7R)-4-Chloro-9,9-dimethyl-2,2,6,6-tetra(3,5-dimethylphenyl)-3,5,8,10-tetraoxa-4-phosphabicyclo[5.3.0]decane: 2R,3R-O-isopropylidene-1,1,4,4-tetra(3,5-dimethylphenyl)threitol (3.50 g, 6.0 mmol) was dried by dissolving the compound in 15 ml of toluene and evaporating thoroughly to dryness (3 times). The diol was dissolved in 60 ml of toluene together with triethylamine (1.3 ml, 9 mmol) and cooled to -40 °C. Subsequently, a solution of phosphorus trichloride (0.66 ml, 7.5 mmol) and triethylamine (1.3 ml, 9 mmol) in 20 ml of toluene was added dropwise. After complete addition, the cooling bath was removed, and the cloudy mixture slowly warmed to room temperature and stirred overnight. Next, the suspension was refluxed for 2 hrs. and filtered under strict nitrogen atmosphere to remove the salts (Et,N.HCl) formed. The resulting solution was evaporated \textit{in vacuo} to yield a slightly yellow moisture-sensitive powder as the product. This was not purified further, but used immediately in the following reactions.
(1R,7R)-4-Diethylamino-9,9-dimethyl-2,2,6,6-tetra(3,5-dimethylphenyl)-3,5,8,10-tetraoxa-4-phosphabicyclo[5.3.0]decane (R,R)-5: To a solution of (1R,7R)-4-chloro-9,9-dimethyl-2,2,6,6-tetra(3,5-dimethylphenyl)-3,5,8,10-tetraoxa-4-phosphabicyclo[5.3.0]decane (2.3 g, 3.5 mmol) in toluene (75 ml) was added dropwise at 0 °C a solution of diethylamine (0.54 ml, 5.3 mmol) and triethylamine (0.73 ml, 5.3 mmol) in toluene (20 ml). After complete addition, the mixture was allowed to warm to room temperature and stirred for 2 hrs. The resulting suspension was filtered under nitrogen and evaporated in vacuo. The resulting off-white powder was purified by column chromatography (hexanes triethylamine 95:5 v:v). Yield: 2.100 g (88%) of white semi-crystalline powder.

1H NMR: δ = 7.51 (s, 2H, Ar-H), 7.29 (s, 2H, Ar-H), 7.15 (s, 4H, Ar-H), 6.92-6.55 (m, 4H, Ar-CH), 5.15 (double d, 1H, J = 8.3, 3.5 Hz, OCH), 4.75 (d, 1H, J = 8.3 Hz, OCH), 3.33 (double q, 4H, J = 11.0 Hz, 7.0 Hz, Ni(CH2CH2)-), 2.35-2.33 (m, 24H, ArCH), 1.50 (s, 3H, OCH3), 1.25 (t, 6H, J = 7.0 Hz, Ni(CH2CH2)-), 0.33 (s, 3H, OCH3); 13C-NMR: δ 147.6, 147.2, 142.3, 137.3, 136.9, 136.7, 136.4, 129.2, 129.0, 128.9, 128.8, 127.2, 126.8, 126.7, 125.3, 111.4, 83.5, 83.1, 82.8, 81.4, 81.3, 81.2, 39.5, 39.2, 28.0, 27.2, 25.6, 21.9, 21.9, 15.7; 31P-NMR: δ 141.5. HRMS (FAB, M-H): calc. for C50H32N8O10P: m/z 860.3869, found: 860.3856; Anal. calc. for C50H32N8O10P: C, 75.96, H, 8.01, N, 2.06; found: C, 75.96, H, 8.01, N, 2.06.

(1S,7S)-4-Diethylamino-9,9-dimethyl-2,2,6,6-tetra(3,5-dimethylphenyl)-3,5,8,10-tetraoxa-4-phosphabicyclo[5.3.0]decane, (S,S)-5: This compound was prepared as described for (R,R)-5.

1H NMR: δ = 7.43 (s, 2H, Ar-H), 7.21 (s, 2H, Ar-H), 7.05 (s, 4H, Ar-H), 6.86-6.82 (m, 4H, Ar-H), 5.08 (double d, 1H, J = 8.3, 3.5 Hz, OCH), 4.67 (d, 1H, J = 8.3 Hz, OCH), 3.26 (double q, 4H, J = 11.0 Hz, 7.0 Hz, Ni(CH2CH2)-), 2.30-2.26 (m, 24H, ArCH), 1.42 (s, 3H, OCH3), 1.17 (t, 6H, J = 7.0 Hz, Ni(CH2CH2)-), 0.25 (s, 3H, OCH3); 13C-NMR: δ 147.6, 147.2, 142.4, 137.3, 136.9, 136.7, 136.4, 129.2, 129.0, 128.8, 128.7, 126.8, 126.7, 125.3, 111.4, 83.5, 83.1, 82.8, 81.4, 81.3, 81.2, 39.3 (d, Jp,C = 22.0 Hz), 28.0, 25.6, 21.8, 15.7, 15.6; 31P-NMR: δ 141.5. HRMS (FAB, M-H): calc. for C50H32N8O10P: m/z 860.3869, found: 860.3856; Anal. calc. for C50H32N8O10P: C, 75.96, H, 8.01, N, 2.06; found: C, 75.96, H, 8.22, N, 2.20.

(1S,7S)-4-(N-methyl-N-(R)-1-phenylethylamino)-9,9-dimethyl-2,2,6,6-tetra(3,5-dimethylphenyl)-3,5,8,10-tetraoxa-4-phosphabicyclo[5.3.0]decane, (S,S,R)-6: Prepared analogously to the synthesis of (R,R)-5 from (1S,7S)-4-Chloro-9,9-dimethyl-2,2,6,6-tetra(3,5-dimethylphenyl)-3,5,8,10-tetraoxa-4-phosphabicyclo[5.3.0]decane (2.6 mmol) and (R)-(+)N,N-dimethylbenzylamine (0.47 ml, 3.2 mmol). The crude product was purified by extraction with hexanes (2 x 10 ml), followed by quick column chromatography (hexanes triethylamine 95:5 v:v) to give a white foam as the product. Yield: 510 mg (27%).
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H NMR: δ 7.69-6.80 (m, 17H, Ar-H), 5.14 (double d, 1H, J = 8.2, 3.2 Hz, OCH3), 4.70 (m, 1H, NCH3), 3.15 (d, 1H, J = 8.2 Hz, OCH3), 2.84-2.13 (m, 24H, Ar-C7H), 1.53 (td, 3H, J = 6.9 Hz, NCH3), 1.47 (s, 3H, OCH3), 0.50 (s, 3H, OCH3). 1\(^{13}\)C; 1H; (C.D.)

NMR: δ = 147.5, 147.1, 143.2, 143.2, 142.6, 142.1, 137.4, 136.9, 136.8, 136.4, 129.3, 128.2, 128.9, 128.2, 128.1, 128.0, 127.2, 126.8, 125.3, 111.5, 83.4, 82.9, 82.7, 81.6, 81.5, 81.4, 55.3 (d, 2Jp,H = 35.4 Hz), 28.0, 26.5, 26.4, 25.7, 21.9, 21.8, 18.4, 18.4, 12.0. 31\(^{13}\)P; 1H; NMR: δ = 141.0. HRMS (FAB + M-H') : calc. for C34H27NO5P: m/z 742.4025, found 742.4025.

(1R,7R)-4-(N-methyl-N-(R)-1-phenylethylamino)-9,9-dimethyl-2,2,6,6-tetra(3,5-dimethylphenyl)-3,5,8,10-tetraoxa-4-phosphabicyclo[5.3.0]decane (1R,7R,8)-6). This compound was prepared similarly to the synthesis of 1(S,S,R)-6 from (1R,7R)-4-Chloro-9,9-dimethyl-2,2,6,6-tetra(3,5-dimethylphenyl)-3,5,8,10-tetraoxa-4-phosphabicyclo[5.3.0]decane (0.81 mmol) and (-S')-N,N'-dimethylbenzylamine (141 µL; 0.97 mmol). Yield: 268 mg (45 %). 1H NMR (C,D3): δ = 8.00 (s, 2H, Ar-H), 7.71 (s, 2H, Ar-H), 7.58 (s, 4H, Ar-H), 7.46 (s, 1H, Ar-H), 7.44 (s, 1H, Ar-H), 7.22-7.07 (m, 4H, Ar-H), 6.77-6.70 (m, 4H, Ar-H), 5.84 (double d, 1H, J = 8.4, 3.9 Hz, OCH3), 5.34 (d, 1H, 2Jp,H = 8.4 Hz, OCH3), 4.84-4.75 (m, 1H, NCH3Me(Ph)), 2.81 (d, 3H, 2Jp,H = 6.3 Hz, NCH3), 2.18-2.07 (m, 24H, Ar-C7H), 1.55 (s, 3H, OCH3), 1.48 (d, 3H, 2Jp,H = 6.9 Hz), 0.49 (s, 3H, OCH3). 13C; 1H; NMR (C.D3): δ = 148.7, 148.1, 144.0, 143.9, 143.5, 143.5, 143.5, 138.0, 137.6, 137.4, 137.4, 137.6, 137.0, 129.9, 129.6, 129.5, 128.9, 128.0, 127.8, 127.7, 127.4, 126.2 (partial overlap with residual solvent signal), 112.1, 84.7, 83.7, 83.4, 82.6, 82.5, 82.5, 56.6 (d, 2Jp,H = 35.4 Hz), 35.3 (m), 29.8, 28.5, 27.6 (m), 26.3, 26.0, 24.9 (m), 19.5, 12.0. 31P; 1H; NMR.
(1S,7S)-4-(N-methyl-N-(S)-1-phenylethylamino)-9,9-dimethyl-2,2,6,6-tetra(3,5-dimethylphenyl)-3,5,8,10-tetraoxa-4-phosphabicyclo[5.3.0]decane. (1S,7S)-6: This compound was prepared similarly to the synthesis of (S,S)-6 from (1S,7S)-4-Chloro-9,9-dimethyl-2,2,6,6-tetra(3,5-dimethylphenyl)-3,5,8,10-tetraoxa-4-phosphabicyclo[5.3.0]decane (0.81 mmol) and (S)-(2)-N,N-dimethylbenzylamine (141 μL; 0.97 mmol). Yield: 261 mg (43%). 1H NMR (CDCl₃); δ = 7.99 (s, 2H, Ar-H), 7.73 (s, 1H, Ar-H), 7.63 (s, 2H, Ar-H), 7.56 (d, 2H, J = 7.7 Hz, Ar-H), 7.22-7.11 (m, 4H, Ar-H), 6.79-6.70 (m, 4H, Ar-H), 5.83 (double d, 1H, J = 8.3, 3.8 Hz, OCH₂), 5.44 (d, 1H, JCH₂ = 8.3 Hz, OCH₂), 4.91-4.83 (m, 1H, NCH₂), 2.77 (d, 3H, JCH₂ = 7.1 Hz, NCH₂), 2.18-2.07 (m, 24H, Ar-CH₂), 1.53 (d, 3H, JCH₂ = 7.1 Hz), 1.52 (s, 3H, OCCH₃), 0.55 (s, 3H, OCCH₃). 13C¹H j NMR: δ = 148.6, 148.1, 143.7, 143.6, 143.5, 143.1, 138.1, 137.6, 137.4, 137.0, 130.0, 129.8, 129.6, 129.4, 127.9, 127.3, 126.1, 112.3, 84.3, 83.8, 83.5, 83.1, 82.5, 82.4, 56.0 (d, JCH₂ = 34.2 Hz), 35.3, 29.8, 28.4, 27.6, 27.3, 27.2, 26.4, 26.0, 23.1, 22.0 (m), 19.0, 12.0. 31P j H NMR (CDCl₃); δ = 142.0. HRMS (FAB + M-H⁺); calc. for C₁₄H₁₄NO₄P: m/z 742.4016; found: 742.4016.

(1R,7R)-4-(Diisopropylamino)-9,9-dimethyl-2,2,6,6-tetraphenyl-3,5,8,10-tetraoxa-4-phosphabicyclo[5.3.0]decane. (1R,7R)-8: This compound was prepared analogously to (R,R)-5 from 2R,3R-O-isopropylidene-1,1,4,4-tetraphenylthreitol. Its observed spectroscopic characteristics match previously reported data.¹¹¹

(1R,7R)-4-Diethylamino-9,9-cyclohexyl-2,2,6,6-tetra(3,5-dimethylphenyl)-3,5,8,10-tetraoxa-4-phosphabicyclo[5.3.0]decane. (1R,7R)-12: ¹H NMR: δ = 7.40 (s, 2H, Ar-H), 7.23 (s, 2H, Ar-H), 7.15 (s, 2H, Ar-H), 7.04 (s, 2H, Ar-H), 6.84-6.80 (m, 4H, Ar-H), 4.97 (double d, 1H, J = 8.5, 3.5 Hz, OCH₂), 4.68 (d, 1H, J = 8.5 Hz, OCH₂), 3.22 (double d, 4H, N(CH₂CH₂)₂), 2.28-2.25 (m, 24H, Ar-CH₂), 1.56-1.49 (m, 4H, OCCH₂), 1.28-1.12 (m, 4H, CH₂), 1.15 (t, 6H, J = 6.9 Hz, N(CH₂CH₂)₂), 0.55-0.45 (m, 1H, CH), 0.35-0.24 (m, 1H, CH). ¹³C¹H j NMR: δ = 147.6, 147.4, 142.5, 142.1, 137.2, 136.8, 136.5, 136.2, 129.1, 128.8, 128.7, 128.6, 127.1, 126.9, 126.8, 125.4, 125.2, 112.1, 82.7, 82.4, 81.9, 81.5, 81.4, 41.9, 39.1 (d, J = 22.0 Hz), 37.5, 35.6, 25.4, 24.6, 24.3, 21.9, 15.6, 15.5, 11.4. ¹³P j H NMR: δ = 141.4. HRMS (FAB + M-H⁺); calc. for C₁₄H₁₀NO₄P: m/z 720.4182; found: 721.4182.

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\((R,7R)-4\)-Diethylamino-9,9-dimethyl-2,2,6,6-tetra(2-naphthyl)-3,5,8,10-tetraoxa-4-phosphabicyclo[5.3.0]decane, \((R,R)-9\): The compound was prepared analogously to the 3,5-(CH\(_2\))\(_2\)C\(_6\)H\(_5\) substituted ligand \((R,R)-5\). Purification was done by column chromatography (SiO\(_2\)) twice using hexanes Et\(_2\)N CH\(_3\)Cl (92.5 5.0 2.5 v v) to yield the compound as a white solid (49 % yield).

\(^1H\) NMR: \(\delta = 8.60\) (s, 1H, Ar-H), 8.21 (s, 1H, Ar-H), 8.12 (s, 1H, Ar-H), 8.05 (s, 1H, Ar-H), 7.91-7.41 (m, 24H, Ar-H), 5.53 (double d, 1H, \(J = 8.5, 3.6\) Hz, OCH), 5.12 (d, 1H, \(J = 8.5\) Hz, OCH), 3.37-3.28 (m, 4H, N(CH\(_2\))\(_2\)), 1.41 (s, 3H, OCH\(_3\)).

\((R,7R)-4,4'-(1-aza-4-oxacyclohexyl)-9,9-dimethyl-2,2,6,6-tetra(3,5-dimethylphenyl)-3,5,8,10-tetraoxa-4-phosphabicyclo[5.3.0]decane, \((R,R)-11\): This compound was prepared analogously to the synthesis of \((R,R)-5\) from \((R,7R)-4\)-Chloro-9,9-dimethyl-2,2,6,6-tetra(3,5-dimethylphenyl)-3,5,8,10-tetraoxa-4-phosphabicyclo[5.3.0]decane (2.6 mmol) and morpholine (164 \(\mu\)L, 164 mg, 1.88 mmol). The crude product was purified by quick column chromatography (hexanes/triethylamine 95 5 v v) to give a white foam as the product. Yield: 510 mg (27%).

\(^1H\) NMR: \(\delta = 7.37\) (s, 2H, Ar-H), 7.20 (s, 2H, Ar-H), 7.03 (s, 2H, Ar-H), 6.99 (s, 2H, Ar-H), 6.87-6.83 (m, 4H, Ar-H), 5.07 (double d, 1H, \(J = 8.4, 3.6\) Hz, OCH), 4.73 (d, 1H, 8.3 Hz), 3.74-3.68 (m, 4H, N(CH\(_2\))(CH\(_3\))\(_2\)), 3.35-3.33 (m, 2H, CH\(_2\)O), 3.21-3.18 (m, 2H, CH\(_2\)O), 2.28-2.26 (m, 24H, Ar-CH\(_2\)). 1.43 (s, 3H, OCC\(_3\)), 0.29 (s, 3H, OCC\(_3\)). \(^1C\) NMR (C,D,): \(\delta = 148.2, 147.9, 147.9, 143.0, 143.0, 138.1, 137.7, 137.4, 137.0, 130.0, 129.8, 129.7, 129.5, 127.8, 127.8, 126.0, 112.7, 83.9, 83.7, 83.6, 83.3, 82.5, 82.4, 68.2 (d, \(J = 4.9\) Hz), 45.0 (d, \(J = 17.1\) Hz), 35.3, 29.7, 28.3, 27.6, 26.5, 22.0, 21.8, 21.2, 19.3, 12.0. \(^31P\) HRMS (FAB\(^-\), M-H\(^+\)): calc. for C\(_{34}H\(_{64\_}\),NO\(_2\),P: m/z 694.3661. found: 694.3670; Anal. calc. for C\(_{34}H\(_{64}\),NO\(_2\),P: C, 74.43, H, 7.55, N, 2.02; found: C, 74.28, H, 7.46, N, 1.94.
chromatography (hexanes: triethylamine 95.5:5 v:v) to give a white foam as the product. Yield: 510 mg (27%).

\[ ^{13} \text{C}^\text{H} \text{NMR (CD}_2\text{Cl}_2) \delta = 148.4, 148.0, 148.0, 143.3, 143.2, 138.0, 137.6, 137.3, 129.9, 129.8, 129.7, 129.4, 127.8, 127.8, 112.6, 84.0, 84.1, 83.7, 83.7, 83.5, 83.4, 82.5, 82.4, 56.7, 47.1 (d, J = 7.3 Hz), 44.8 (d, J = 19.5 Hz), 35.3, 29.8, 28.3, 27.6, 26.5, 26.0, 21.9 (m)), 12.0, HRMS (FAB', M-H'): calcd. for C\textsubscript{44}H\textsubscript{44}N\textsubscript{2}O\textsubscript{2}P: m/z 707.3978. found: 707.3986; Anal. calc. for C\textsubscript{44}H\textsubscript{44}N\textsubscript{2}O\textsubscript{2}P: C 74.76, H 7.84, N 3.96; found: C 74.83, H 8.04, N 3.66.

\[(R,R)-4-\text{[}(1R,2S,5S)-2-\text{i}so\text{propyl}-5-\text{methylcyclohexyl}]-9,9-\text{dimethyl}-2,2,6,6-\text{t}etra(3,5\text{-dimethylphenyl})-3,5,8,10-\text{tetraoxa}-4\text{-phosphabicyclo[5.3.0]decan (M-H)}\text{-13:}\] This compound was prepared from (1R,7R)-4-chloro-9,9-dimethyl-2,2,6,6-tetra(3,5-dimethylphenyl)-3,5,8,10-tetraoxa-4-phosphabicyclo[5.3.0]decan (669 mg, 1.04 mmol) and L-(-)-menthol (171 mg, 1.09 mmol). Purification by column chromatography (SiO\textsubscript{2}), Et\textsubscript{2}N hexane = 2.97.5 afforded 330 mg (R,R)-13 as a white powder (40 \text{\% yield}).

\[ ^{1} \text{H NMR (CDCl\textsubscript{3}) } \delta = 7.28 (s, 2H, Ar-H), 7.18 (s, 2H, Ar-H), 7.09 (s, 2H, Ar-H), 7.06 (s, 2H, Ar-H), 6.88 (s, 2H, Ar-H), 6.83 (s, 1H, Ar-H), 5.10 (dd, 1H, J = 8.2, 2.5 Hz, COCH\textsubscript{3}), 4.97 (d, 1H, J = 8.2 Hz, COCH\textsubscript{3}), 4.05-3.95 (m, 1H, POCH), 2.29-2.27 (m, 26H, Ar-CH\textsubscript{2}), 1.63-0.84 (multiple m, 17H), 0.66 (d, 2H, J = 6.9 Hz), 0.38 (s, 3H); ^{13} \text{C}^\text{H} \text{NMR (CDCl\textsubscript{3}) } \delta = 146.7, 146.1, 142.3, 141.6, 137.4, 136.9, 136.6, 136.4, 129.5, 129.1, 128.9, 127.1, 126.9, 126.8, 125.5, 125.2, 112.4, 83.9, 83.8, 82.6, 82.6, 82.3, 82.1, 77.5, 48.7, 48.6, 44.3, 34.9, 34.5, 32.1, 31.8, 29.3, 27.9, 27.7, 27.2, 26.1, 25.6, 25.5, 23.3, 22.9, 22.4, 21.9, 21.7, 21.2, 16.1, 14.4, 11.7; ^{31} \text{P}^\text{H} \text{NMR (CDCl\textsubscript{3}) } \delta = 144.5. \text{HRMS (FAB', M-H')}: \text{calcd. for C}_{41}\text{H}_{44}\text{N}_{2}O_{2}P: m/z 763.4491. found: 763.4465. Anal. calc. for C_{41}H_{44}N_{2}O_{2}P: C 77.13, H 8.32; found: C 76.94, H 8.39.

**Complex Synthesis**

\[ [\text{Pd}(R,R)-5-(4-CNC}_6\text{H}_4)(\mu-\text{Br})]_2: \text{A 50 mL Schlenk vessel equipped with a stirring bar was charged with Pd(dba)_2 (100 mg, 0.174 mol), ligand (474 mg, 0.70 mmol, 4.0 equiv.), and 4-bromobenzonitrile (317 mg, 1.74 mmol, 10 equiv.) and brought under an inert atmosphere. Then, 15 mL toluene was added and the resulting deep purple solution was stirred for 2 hours at room temperature. During this time, the colour of the solution changed to bright yellow, with the concomitant formation of a small amount of Pd-metal. Next, the solution was filtered over Celite and the solvent evaporated in vacuo. The resulting yellow white powder was washed with hexanes (4 x 10 mL), followed by diethyl ether hexanes (1:1 v:v) (4 x 10 mL). After drying under vacuum an off-white powder was obtained. Yield: 65 mg (43 \text{\% yield}).

\[ ^{1} \text{H NMR (CDCl\textsubscript{3}) } \delta = 7.78-6.72 (m, 14H, Ar-H), 5.92-5.76 (bm, 2H), 5.32-5.08 (bm, 2H), 3.27 (bs, 2H), 2.80-2.05 (m, 26H), 1.29-0.75 (m, 6H), 0.59 (bs, 3H), 0.32 (bs, 3H). \text{No significant sharpening was observed.} \]
observed within the range 40 - 50 °C. Above this temperature decomposition occurred: $^1$P; $^1$H;
NMR: $\delta = 93.0, 92.7$ (major signal), 92.2, 90.5. (Apparently, in solution the complex exists as a
mixture of different isomeric complexes. This was at least partially caused by some Br' CT
exchange which had occurred, probably from the CHCl. Because the crystals were grown from
this batch, some of the bromide anions in the crystal structure have been replaced by chloride. This
has no effect on the geometrical outcome and conclusions derived from the analysis).

Crystals suitable for an X-ray analysis were grown from a diethylether hexane solution by slow
evaporation of the solvent.

**Asymmetric Heck Reactions**

**Representative procedure:** Pd(dba)$_2$ (3.8 mg, 0.0066 mmol) and ligand 5 (18 mg, 0.026 mmol,
4 equiv.) were dissolved in 4 ml of dry toluene and stirred at 40 °C for 20 minutes, during which
the solution changed colour from deep purple to orange-yellow. Next, the solution was cooled to
room temperature. N,N-disopropylethyamine (115 µL, 0.66 mmol) was added, followed by
cyclohex-1-ene-carboxylic acid (2-iodophenyl)-methyl-amide (112 mg, 0.33 mmol). The solution
turned bright yellow immediately, and a white precipitate formed. Aliquots were taken from the
mixture at regular intervals, diluted with diethylether and washed with saturated aqueous
ammonium chloride solution and analysed by GC after drying with MgSO$_4$. After 90 minutes, the
reaction mixture was diluted with 15 mL diethylether and washed with saturated aqueous
ammonium chloride, water and subsequently dried over MgSO$_4$. After evaporation of the volatiles
in vacuo the resulting yellow oil was analysed by $^1$H NMR to determine the regioselectivity of the
reaction (integration of signals at 6.13 or 5.29 ppm (cyclohex-2-ene-N-methyl oxindole) compared
with signals at 5.88 ppm (starting material with cyclohex-3-ene-N-methyl oxindole). Pure product
was obtained by column chromatography (SiO$_2$. EtOAc:PE 60:80 = 1:3). The enantiomeric excess
was determined by chiral HPLC (Chiralcel OD. hexane 1-propanol 96:4, flow 0.35 mL min.. UV
254 nm. $t_R$ cyclohex-2-ene-N-methyl oxindole = 19.21 ((R)-enantiomer).$^{[40]}$ 22.25 min.; $t_R$
cyclohex-3-ene-N-methyl oxindole = 16.80, (major enantiomer with (R,R)-5) 17.65 min.

**X-ray crystal structure determination of cis-[Pd((R,R)-5)(4-CNC$_4$H$_4$)(µ-Br)];**

C$_{30}$H$_{30}$Br$_2$N$_2$Cl$_{1.2}$N,O,P,Pd: - solvent. Fw = 1913.19 [*], yellow block, 0.45 x 0.30 x 0.15 mm$^3$.
Tetragonal crystal system. space group P4$_2$2$_1$2 (no. 92). Cell parameters: a = b = 17.1829(1) Å, c =
35.1646(3) Å. V = 10382.42(12) Å$^3$. Z = 4. p = 1.224 g cm$^{-3}$ [*]. 64436 reflections were measured
on a Nonius KappaCCD diffractometer with rotating anode and Mo-K$_\alpha$ radiation (graphite
monochromator. $\lambda = 0.71073$ Å) at a temperature of 150 K. An absorption correction based on
multiple measured reflections was applied ($ε = 1.01$ mm$^{-1}$ [*]. 0.73-0.81 transmission). The
reflections were merged using the program SORTAV.$^{[35]}$. resulting in 8937 unique reflections (R$_{int}$}
of which 7696 were observed \( |I| > 2\sigma(I)\). The structure was solved with automated
Patterson methods using the program DIRDIF \(^{21}\), and refined with the program SHELXL97 \(^{21}\)
against \( F^2 \) of all reflections up to a resolution of \( (\sin \theta / \lambda)_{\text{max}} = 0.59 \text{ Å} \). Non hydrogen atoms were
refined freely with anisotropic displacement parameters, hydrogen atoms were refined as rigid
groups. The halogen positions were occupied with \( 82\% \text{Br} \ 18\% \text{Cl} \) for Br1 Cl1 and 65\%Br
35\%Cl for Br2 Cl2. They were constrained to the same positions and the same displacement
parameters, respectively. One mesityl group was rotationally disordered and refined with a disorder
model. The Flack parameter \(^{21}\) refined to a value of \( x = 0.02(8) \). The crystal structure contains
large voids (1407.3 Å \(^3\) unit cell), which were filled with disordered solvent molecules. Their
contribution to the structure factors was secured by back-Fourier transformation (program
PLATON \(^{20}\), routine SQUEEZE, 101 electrons unit cell). 609 refined parameters, 108 restraints.
\( R \) (obs. refl.): \( R_1 = 0.0313 \), \( wR_2 = 0.0723 \). \( R \) (all data): \( R_1 = 0.0404 \), \( wR_2 = 0.0762 \). Weighting
Scheme \( w = 1 [\sigma(F)^2 - (0.0432P)^2 - 0.2572P] \), where \( P = (F^2 - 2F_e) / 3 \). GoF = 1.041. Residual
electron density between 0.28 and 0.25 e Å\(^{-3}\). The drawings, structure calculations, and checking
for higher symmetry was performed with the program PLATON \(^{20}\).

[*] Derived values do not contain the contribution of the disordered solvent molecules.

**Table 6.** Selected crystal data and details of the structure determination of \( \text{cis-}[\text{Pd}((R,R)-5)(4-\text{CNC},\text{H}_4\text{H})(\mu-\text{Br})]_2 \)

<table>
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<th>Crystal data</th>
<th>Data collection</th>
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</thead>
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<td><strong>Formula</strong></td>
<td>( \text{C}<em>{19}\text{H}</em>{15}\text{Br}<em>{11}\text{Cl}</em>{10}\text{N}<em>{10}\text{O}</em>{10}\text{P}<em>{2}\text{Pd}</em>{2} )</td>
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<td><strong>Molecular Weight</strong></td>
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<tr>
<td><strong>Crystal system</strong></td>
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<tr>
<td><strong>b (Å)</strong></td>
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</tr>
<tr>
<td><strong>c (Å)</strong></td>
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</tr>
<tr>
<td><strong>Z</strong></td>
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</tr>
<tr>
<td><strong>V (Å(^3))</strong></td>
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<tr>
<td><strong>D (g cm(^{-3}))</strong></td>
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<tr>
<td><strong>( \mu ) (Mo-K(_\alpha)) (mm(^{-1}))</strong></td>
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**References:**


Fast Asymmetric Heck Reactions using Phosphoramidites


