Phosphoramidite ligands and artificial metalloenzymes in enantioselective rhodium-catalysis
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Chapter 2
Enantioselective Rh-Catalyzed Hydrogenation of Enol Acetates and Enol Carbamates with Monodentate Phosphoramidites

Monodentate phosphoramidites, in particular PipPhos and its octahydro analogue, are excellent ligands for the rhodium-catalyzed asymmetric hydrogenation of aromatic enol acetates, enol carbamates and 2-dienol carbamates in up to 98% ee. These latter substrates were hydrogenated selectively to the carbamates of the allyl alcohol.

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Chapter 2

2.1 Introduction

Homogeneous asymmetric hydrogenation of prochiral olefins has proven to be one of the most powerful tools in asymmetric catalysis.\textsuperscript{1,2} In most of the cases, only solvent, substrate, hydrogen and a small amount of catalyst are needed, making this technology clean and atom-efficient.\textsuperscript{3} In particular, the combination of rhodium and phosphorus based chiral ligands has proven to be essential for the development and fast advances in homogeneous asymmetric hydrogenation.\textsuperscript{4} In Scheme 2.1 some representative classes of olefins used as substrates are depicted. In many cases, the reaction is performed at room temperature using only moderate hydrogen pressure. Neither bases, nor acids are usually required, providing mild operational conditions that allow the presence of sensitive functionalities.

\begin{center}
\textbf{Scheme 2.1} Classes of prochiral olefins used in Rh-catalyzed asymmetric hydrogenation
\end{center}

Chiral alcohols are important building blocks and development of enantioselective procedures that allows their preparation with a minimum amount of waste or additives and with a large substrate scope is highly desirable.

As discussed in Chapter 1, an important contribution to the homogeneous asymmetric hydrogenation field is provided by the ruthenium-catalyzed asymmetric hydrogenation of prochiral ketones for the preparation of chiral alcohols. Ru-catalysts are based on bis-phosphine and diamine ligands. Variation of the bis-phosphine is cumbersome because of lengthy syntheses and extensive purifications. Therefore, in order to be able to rapidly find a higher enantioselective catalyst for a new substrate it would be highly advantageous to have a catalyst based on simple monodentate ligands, such as phosphoramidites, phosphites or phosphonites that can be easily made even using a robotic system.\textsuperscript{5}

2.2 Hydrogenation of enol acetates

The asymmetric hydrogenation of enol acetates 2.5 gives access to chiral esters 2.6, which makes this method an interesting alternative to the enantioselective hydrogenation of prochiral ketones for the preparation of chiral alcohols 2.7 (Scheme 2.2).
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Scheme 2.2  Alternative pathway for the preparation of chiral alcohols

Very few ligands have been reported to be successful for this transformation in spite of the structural similarity with enamides 2.1, the majority of which can be hydrogenated with high enantioselectivities. Modest enantioselectivities (up to 81% ee) were reached until Burk reported the hydrogenation of simple enol acetates such as 2.5a (89% ee) and 2.5c (90% ee) using DuPHOS (L3) and BPE (L4) ligands (Scheme 2.3). In one of the most recent examples (Scheme 2.3), enantioselectivities up to 99% ee were achieved using Rh-TangPhos (L1) for the hydrogenation of aromatic acyclic enol acetates.

Scheme 2.3  Acyclic aromatic vinyl acetates 2.5a-c as hydrogenation substrates

Catalysts such as Ru-TunaPhos (L2) and Rh-PennPhos (L5) were found to be more efficient for cyclic enol acetates such as 2.8 (up to 99% ee). The most significant results are depicted in Scheme 2.4.
In most cases, reaction times between 12 and 14 h have been reported and the substrate scope is limited to aryl enol acetates. Boaz reported the only example of the use of a chiral bidentate phosphine ligand in the Rh-catalyzed asymmetric hydrogenation of aliphatic enol acetates. Using bidentate DuPHOS (L3), 64% ee and 77% ee were obtained in the hydrogenation of simple aliphatic enol acetates 2.10a-b (Scheme 2.5). Moreover, in this case reaction times of 2 h using 2 bar H₂ were reported. The enantioselectivities are modest compared to what has been achieved with 2-aryl enol acetates 2.5a and 2.5c, confirming the fact that aliphatic substrates are more difficult to hydrogenate with high enantioselectivities, as observed when using other methodologies (see Chapter 1). Much higher enantioselectivities where instead obtained in the hydrogenation of 1-alkenyl 2.12a-b and 1-alkynyl enol acetates 2.14a-b (Scheme 2.5). Whether this increase in enantioselectivity was due to reduced steric hindrance or coordination of the extra unsaturated moiety (alkene, acetylene) to the metal center was not clarified.
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Scheme 2.5  Hydrogenation of enol acetates bearing 1-alkyl (2.10a-b), 1-alkenyl (2.12a-b) or 1-alkynyl (2.14a-b) substituents using DuPHOS (L3).

Reetz and coworkers recently reported the only example so far of a successful use of monodentate ligands (Scheme 2.6). Enantioselectivities up to 90% ee were found at room temperature (94% ee at -20 °C) for the more difficult alkenyl carboxylate 2.16, using a carbohydrate-derived Rh-monophosphite catalyst, containing two sources of chirality (L6a-b).

Scheme 2.6  Hydrogenation of alkyl vinyl carboxylates with monodentate phosphite ligands

The presence of the furanyl group in 2.16 seemed to be essential, as lower enantioselectivity was obtained with the more common aliphatic vinyl acetate 2.18.
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(Scheme 2.6). Catalyst L6a appeared to be quite stable and active, as its loading was in one example reduced to 0.2%. Nevertheless, no attempts were reported on the use of reduced hydrogen pressure and no information was given on the actual speed of the reaction. In addition, Reetz and coworkers reported that the use of BINOL-derived phosphoramidites in combination with enol ester 2.16 afforded only <10% of the product 2.17. A possible explanation for the slow development in this area might be due to the weaker coordination of the acyl group of the enol ester to the metal as compared to the enamides, where it is well known that this secondary coordination is important for the enantiodiscrimination (Scheme 2.7).

Scheme 2.7   *Substrate chelating features and catalyst-substrate interactions*

2.3  Earlier work and aim of this study

In view of the excellent results we have previously obtained with BINOL-derived monodentate phosphoramidites (Scheme 2.8) in the Rh-catalyzed hydrogenation of a variety of prochiral olefins 2.1-2.4 (Scheme 2.1), we became intrigued with the idea of applying these ligands to the more challenging enol acetates 2.5.

We also envisaged the use of enol carbamates 2.20, as it was believed that the increased electron density would improve the binding capabilities of the substrate to the metal center and make it more akin to an enamide (Scheme 2.9).

Scheme 2.8   General structure of the BINOL-derived monodentate phosphoramidite ligands used in this study

Scheme 2.9  *Substrates with bidentate structural features*
Enantioselective Rh-Catalyzed Hydrogenation of Enol Acetates and Enol Carbamates with Monodentate Phosphoramidites

Simple 1-phenyl-vinyl acetate (2.5a) and 1-phenyl-vinyl N,N-dimethylcarbamate (2.21) have been tested in a couple of occasions in our research group using Monophos™ (A1),13 (R)-α-methylbenzylamine based phosphoramidite (A2)14 and t-Bu(Ph)(H)PO (L7),15 as chiral ligands. The not encouraging results are depicted in Table 2.1.

Surprisingly, MonoPhos™ (A1, Table 2.1, entry 1) induced a low 8% ee in the hydrogenation of 2.5a without reaching full conversion. Faster reaction but equally poor enantioselectivity was achieved with ligand A2 (entry 2). The hydrogenation of enol carbamate 2.21 also afforded 2.22 with rather poor, although definitely higher, enantioselectivities (entries 3 and 4). The use of SPO ligand L7 seemed to be more promising as 81% ee could be obtained, but the reaction time was very long and improvement on the reactivity could not be obtained. When using this class of chiral ligands, increase in H₂ pressure had a negative effect on both reactivity and enantioselectivity.16

Table 2.1 Previous attempts of asymmetric hydrogenation of enol esters and carbamates using monodentate ligands

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>ligand</th>
<th>Rh(l)</th>
<th>pH₂ (bar)</th>
<th>time (h)</th>
<th>conv.(%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.5a</td>
<td>(S)-A1</td>
<td>Rh(COD)₂BF₄</td>
<td>5</td>
<td>19</td>
<td>95</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>2.5a</td>
<td>(S,R)-A2</td>
<td>Rh(COD)₂BF₄</td>
<td>1</td>
<td>0.25</td>
<td>75</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
<td>2.21</td>
<td>(S)-A1</td>
<td>Rh(COD)₂BF₄</td>
<td>5</td>
<td>20</td>
<td>&gt;99</td>
<td>17</td>
</tr>
<tr>
<td>4</td>
<td>2.21</td>
<td>(S,R)-A2</td>
<td>Rh(NBD)₂BF₄</td>
<td>5</td>
<td>15</td>
<td>&gt;99</td>
<td>36</td>
</tr>
<tr>
<td>5</td>
<td>2.21</td>
<td>(R)-L7</td>
<td>Rh(NBD)₂BF₄</td>
<td>1</td>
<td>64</td>
<td>&gt;99</td>
<td>81</td>
</tr>
</tbody>
</table>

aDCM, rt. bS/C= 27. cS/C= 100. dS/C= 21. eEtOAc used as solvent.

These preliminary results seemed to confirm that enol acetate 2.5a is a challenging substrate in Rh-catalyzed hydrogenation also using monodentate phosphoramidite.
ligands. The outcome of these experiments seemed somehow to contradict what was reported by Reetz and coworkers,\textsuperscript{10} at least in terms of activity, although taking into account that the substrate they refer to is different (2.16, Scheme 2.6). Despite the modest results, the Rh-catalyzed asymmetric hydrogenation of enol carbamate 2.21 seemed to hold promise.

The aim of this study was to explore the potential suitability of enol acetates 2.5 and enol carbamates 2.20 as substrates for Rh-catalyzed asymmetric hydrogenation in combination with monodentate phosphoramidites (Scheme 2.8) as chiral ligands.

\subsection*{2.4 Synthesis of 1-aryl-vinyl acetates}

The most straightforward and generally applied preparation of the aromatic enol acetates 2.5 is the procedure described by House and coworkers.\textsuperscript{17} It involves the acid catalyzed enolization of the corresponding ketone 2.23 and capture of the enol with isopropenyl acetate (2.24) by transesterification (Scheme 2.10).

\begin{center}
\begin{tikzpicture}
\node (a) at (0,0) {\textbf{2.23a-c}};
\node (b) at (3,0) {\textbf{2.5a-c}};
\node (c) at (1.5,-2.5) {\textbf{2.5a}};
\node (d) at (1.5,-3.5) {\textbf{2.5b}};
\node (e) at (1.5,-4.5) {\textbf{2.5c}};
\node (f) at (1.5,-2.25) {64\% yield};
\node (g) at (1.5,-3.3) {63\% yield};
\node (h) at (1.5,-4.3) {60\% yield};
\draw[->] (a) -- (b);
\draw[->] (a) -- (c);
\draw[->] (a) -- (d);
\draw[->] (a) -- (e);
\draw[->] (c) -- (b);
\draw[->] (d) -- (b);
\draw[->] (e) -- (b);
\end{tikzpicture}
\end{center}

\textbf{Scheme 2.10} \hspace{1cm} \textit{Synthesis of 1-aryl-vinyl acetates 2.5a-c}

Compounds 2.5a-c were prepared according to this literature procedure and isolated by fractional distillation under reduced pressure (2.5a, 2.5b) or silica gel flash chromatography (2.5c). The reaction relies on the tautomerism between ketones possessing an $\alpha$-hydrogen and their enols and is particularly suitable for aryl ketones 2.23, since only one product is obtained from their acylation. Nevertheless, it is of limited scope, as different regioisomers would be obtained whenever dialkyl ketones 2.18 would be used as starting material. An example reported by House is shown in Scheme 2.11.\textsuperscript{18}
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Scheme 2.11  Mixture of enol acetates obtained from asymmetric dialkyl ketones

The terminal enol acetate 2.25c, the most suitable of these regioisomers for hydrogenation purposes, turned out to be the less abundant product. In this case a valuable alternative would be the regiocontrolled Ru-catalyzed addition of carboxylic acids to alkynes, first reported by Dixneuf and coworkers and more recently by Goossen and coworkers (Scheme 2.12). Ishii and coworkers also reported a similar Ir-catalyzed reaction.

Scheme 2.12  Regiocontrolled Ru-catalyzed synthesis of enol acetates

The use of different reaction conditions (ligand and additives) allowed almost exclusively either the less substituted (with terminal double bond) or the more substituted (with internal double bond) products to be obtained. This method is limited only by the availability of the alkynes.

2.5 Asymmetric hydrogenation of 1-aryl-vinyl acetates

To establish the activity and selectivity of phosphoramidite-based catalysts, initial hydrogenation experiments were performed on the simple 1-phenyl-vinyl acetate (2.5a) using three different phosphoramidites A1, A3, A4 (Scheme 2.13).

Scheme 2.13  Monodentate phosphoramidites used for the Rh-catalyzed asymmetric hydrogenation of vinyl acetates 2.5a-c
MonoPhos™ (A1) was used as a reference to the earlier work (Table 2.1). PipPhos (A3) and MorfPhos (A4) were chosen because they have recently been proven able to improve the already excellent performances of MonoPhos™ for many classes of substrates.\textsuperscript{12a} The initial conditions used are those established in the hydrogenation of standard dehydroamino esters (2.2) whilst using MonoPhos™ as chiral ligand (Chapter 1) and the results are depicted in Table 2.2.\textsuperscript{21}

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand</th>
<th>conv\textsuperscript{ab} (%)</th>
<th>ee\textsuperscript{c} (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(S)-A1</td>
<td>89</td>
<td>10 (R)</td>
</tr>
<tr>
<td>2</td>
<td>(S)-A3</td>
<td>97</td>
<td>90 (R)</td>
</tr>
<tr>
<td>3</td>
<td>(S)-A4</td>
<td>90</td>
<td>66 (R)</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Reactions performed in 4 mL of solvent with 0.2 mmol of substrate and 1 mol\% of catalyst at rt for 16 h. \textsuperscript{b}Conversions determined by \textsuperscript{1}H NMR and GC. \textsuperscript{c}ee’s determined by chiral GC.

As expected, and in line with the previous results, MonoPhos™ (A1) induced only 10% ee without reaching full conversion (Table 2.2, entry 1). On the contrary, an exciting 90% ee was obtained by using PipPhos (A3, entry 2), whilst ligand A4 gave again a modest result (entry 3). In all cases, full conversion was not achieved, but luckily the ligand that provided the best enantioselectivity also induced the highest rate. In order to reach full conversion and to determine if higher H\textsubscript{2} pressure would speed up the reaction without compromising the enantioselectivity, experiments at different H\textsubscript{2} pressure were performed (Table 2.3). The same solvent, temperature and catalyst loading were used, and it was decided to concentrate on ligand A3, due to its superior performance.

At higher hydrogen pressure, an increase in activity and no decrease in enantioselectivity were observed, in agreement with what was reported for other classes of substrates (2.1-2.4) using chiral phosphoramidite ligands. According to the H\textsubscript{2} uptake, full conversion was reached in around 8 hours at 10 bar H\textsubscript{2} (Table 2.3, entry 2) and in around 4 hours at 25 bar H\textsubscript{2} (entry 4) using 1 mol\% of catalyst.
Table 2.3  

Hydrogenation of 1-phenyl-vinyl acetate (2.5a) at different H₂ pressure

<table>
<thead>
<tr>
<th>entry</th>
<th>pressure H₂ (bar)</th>
<th>conversion a,b (%)</th>
<th>ee c (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5</td>
<td>97</td>
<td>90 (R)</td>
</tr>
<tr>
<td>2</td>
<td>10</td>
<td>100</td>
<td>90 (R)</td>
</tr>
<tr>
<td>3</td>
<td>20</td>
<td>100</td>
<td>91 (R)</td>
</tr>
<tr>
<td>4</td>
<td>25</td>
<td>100</td>
<td>91 (R)</td>
</tr>
</tbody>
</table>

aReactions performed in 4 mL of solvent with 0.2 mmol of substrate and 1 mol% of catalyst at rt for 16 h. bConversions determined by ¹H NMR and GC. cee’s determined by chiral GC.

A number of experiments using different solvents were performed, in order to determine if this had any influence on reactivity and enantioselectivity. The results are depicted in Table 2.4 and the solvents are listed in order of increasing polarity.

Table 2.4  

Hydrogenation of 1-phenyl-vinyl acetate (2.5a) in different solvents

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent (polarity index)</th>
<th>conversion a,b (%)</th>
<th>ee c (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Toluene (2.4)</td>
<td>7</td>
<td>racemic</td>
</tr>
<tr>
<td>2</td>
<td>DCM (3.1)</td>
<td>100</td>
<td>91 (R)</td>
</tr>
<tr>
<td>3</td>
<td>i-PrOH (3.9)</td>
<td>100</td>
<td>10 (R)</td>
</tr>
<tr>
<td>4</td>
<td>THF (4.0)</td>
<td>61</td>
<td>racemic</td>
</tr>
<tr>
<td>5</td>
<td>EtOAc (4.4)</td>
<td>56</td>
<td>9 (R)</td>
</tr>
<tr>
<td>6</td>
<td>MeOH (5.1)</td>
<td>92</td>
<td>26 (S)</td>
</tr>
</tbody>
</table>

aReactions performed in 4 mL of solvent with 0.2 mmol of substrate and 1 mol% of catalyst at rt for 16 h. bConversions determined by ¹H NMR and GC. cee’s determined by chiral GC.

dIn all cases, the (S)-enantiomer of the ligand was used.

The results depicted in Table 2.4 unequivocally established that CH₂Cl₂ was the best in terms of both reactivity and enantioselectivity, similar to most phosphoramidite-based hydrogenations, but the solvent dependency is more...
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dramatic in the present system (entry 2). The influence of the solvent is very strong as none of the results obtained with the other solvents are even slightly comparable with CH₂Cl₂, as is usually the case in the hydrogenation of other classes of substrates. Moreover, using MeOH as solvent, the opposite enantiomer of 2.6a (26% ee) was obtained. No relation between the results and the polarity of the solvents could be deduced. A possible explanation for such a clear preference could be found in the lack of competition between CH₂Cl₂ and the substrate in the coordination with the metal complex, compared to all the other solvents. This would confirm the assumption that enol acetates 2.5 have limited coordinating capabilities compared to other classes of substrates, which can be successfully hydrogenated with high enantioselectivities using a variety of catalytic systems.4

The other 1-aryl-vinyl acetates synthesized (2.5b-c) were also studied using A3 and A4 as chiral ligands and CH₂Cl₂ as solvent. The results are listed in Table 2.5.

Table 2.5  Hydrogenation of 1-aryl-vinyl acetates 2.5b-c

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>product</th>
<th>ligand</th>
<th>conversion&lt;sup&gt;a,b&lt;/sup&gt; (%)</th>
<th>ee&lt;sup&gt;c&lt;/sup&gt; (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.5b</td>
<td>2.6b</td>
<td>(S)-A3</td>
<td>74</td>
<td>78 (R)</td>
</tr>
<tr>
<td>2</td>
<td>2.5b&lt;sup&gt;d&lt;/sup&gt;</td>
<td>2.6b</td>
<td>(S)-A3</td>
<td>92</td>
<td>90 (R)</td>
</tr>
<tr>
<td>3</td>
<td>2.5b</td>
<td>2.6b</td>
<td>(S)-A4</td>
<td>32</td>
<td>29 (R)</td>
</tr>
<tr>
<td>4</td>
<td>2.5c</td>
<td>2.6c</td>
<td>(S)-A3</td>
<td>100</td>
<td>98 (R)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Reactions performed in 4 mL of solvent with 0.2 mmol of substrate and 1 mol% of catalyst at rt for 16 h.  
<sup>b</sup>Conversions determined by <sup>1</sup>H NMR and GC.  
<sup>c</sup>ees determined by chiral GC.  
<sup>d</sup>Reaction carried out at 20 bar H₂.

Good selectivity but somewhat lower reactivity was observed using ligand A3 with 1-p-Cl-phenyl-vinyl acetate (2.5b). Even using 20 bar H₂ pressure, full conversion was not achieved, but an increase in enantioselectivity was obtained (Table 2.5, entries 1 and 2). Lower reactivity for substrate 2.5b was previously observed using a Ru-TunaPhos (L2) catalyst (48 h). In contrast, an excellent 98% ee with higher reactivity (entry 4) was obtained with 1-p-NO₂-phenyl-vinyl acetate (2.5c) even using 5 bar H₂ pressure.

The outcome of this preliminary investigation showed that monodentate phosphoramidites are indeed suitable ligands for the Rh-catalyzed asymmetric hydrogenation of aromatic vinyl carboxylates 2.5a-c. The use of CH₂Cl₂ as the
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solvent and PipPhos (A3) as the chiral ligand seemed so far to be essential. Even small structural changes (ligands A3 and A4) induced remarkably different results as shown in Table 2.2 (entries 2 vs 3) and Table 2.5 (entries 1 vs 3).

Subsequently, it was decided to test the assumptions regarding the superiority of vinyl carbamates 2.20 as substrates for asymmetric hydrogenation, due to their supposed higher electron density and therefore better coordination capabilities.

2.6 Synthesis of 1-phenyl-vinyl N,N-dialkyl carbamates
Vinyl carbamates are known to be useful intermediates for the preparation of agricultural chemicals, pharmaceutical intermediates or precursors for polymers. Vinyl carbamates have been prepared by addition of amines to vinyl chloroformates, or by dehydrohalogenation of α-halogeno and β-halogenoalkyl carbamates. Nevertheless, all these procedures imply at some stage the use of phosgene. Dixneuf and coworkers reported an interesting alternative synthesis catalyzed by Ru complexes (Scheme 2.14) that unfortunately did not afford the regioisomer 2.20 as the main product, which would be more interesting as substrate for Rh-catalyzed asymmetric hydrogenation.

\[
\text{Scheme 2.14 } \quad \text{Alternative synthesis of vinyl carbamates}
\]

Once more, the most convenient pathway seemed to be the preparation of simple 1-phenyl-vinyl N,N-dialkyl carbamates from the corresponding ketones, in this case by reacting their enolates with carbamoyl chlorides (Scheme 2.15).

\[
\text{Scheme 2.15 } \quad \text{Vinyl carbamates by quenching of the corresponding enolates}
\]

As the enolate needed to be formed quantitatively by using suitable bases, a number of factors needed to be taken into account. Enolates are ambivalent nucleophiles, so the most obvious side product of this procedure is the dicarbonyl compound derived from competitive C-acylation. Minimization of this side reaction...
can be achieved by a proper choice of solvent, co-solvent and metal counter-ion, which parameter also influence the reactivity.\textsuperscript{24} Polar aprotic solvents such as DMSO, DMF, \textit{N}-methylpyrrolidone and HMPA are known to be good cation solvators and poor anion solvators. This means that alkali metal counter-ions (Li\textsuperscript{+}, Na\textsuperscript{+}, K\textsuperscript{+}), which are very sensitive to the aggregation state, will be strongly solvated leaving a \textit{pseudo} bare and more reactive enolate. Moreover, O-acylation will be also enhanced by these conditions. On the other side, solvents like THF and DME, in which the enolate is less reactive but more stable, facilitate product work-up, making them a desirable choice. Nevertheless, the reactivity and regioselectivity can be regained by the addition of co-solvents such as HMPA and TMEDA.

Scheme 2.16 describes the two methods adopted for the synthesis of \textit{N,N}-dimethyl (2.21), \textit{N,N}-diethyl (2.28) and \textit{N,N}-diisopropyl (2.31) substituted 1-phenyl-vinyl carbamates, which were obtained in moderate yields.

**Method A**

\[
\text{SO}_2 \overset{\text{NaH}}{\longrightarrow} \text{S}^- \overset{\text{DMSO}}{\longrightarrow} \text{ONa} \overset{\text{Cl}}{\longrightarrow} \text{ON} \rightarrow \text{R} \quad \text{2.26, R= Me, 37\% yield, 2.27, R= Et, 39\% yield}
\]

**Method B**

\[
\text{MeLi} \overset{\text{THF, rt}}{\longrightarrow} \text{OLi} \overset{\text{THF/HMPA}}{\longrightarrow} \text{2.29, 2.30, 2.31, R= i-Pr, 49\% yield}
\]

**Scheme 2.16** *Synthesis of 1-phenyl-vinyl \textit{N,N}-dialkyl carbamates*

In the first approach (Scheme 2.16, method A), DMSO was used both as reagent and as solvent. The methyl sulfynyl carbanion 2.26 ("dimethyl anion") was formed by reaction of the solvent with NaH at 55 °C. Corey and coworkers first reported the versatility and reactivity of this base in organic synthesis.\textsuperscript{25} It should be noted that the temperature should not exceed 70 °C, otherwise decomposition occurs, which is induced also by prolonged reaction times. Upon addition of acetophenone, the conjugated base of DMSO afforded the corresponding sodium enolate derivative.
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2.27, which was trapped with the desired carbamoyl chloride affording 2.21 and 2.28. The moderate yield could be attributed to the competing C-acylation, but also to the formation of a hydroxyl sulfoxide adduct. In the second approach (Scheme 2.16, method B), a procedure developed by Olofson and coworkers for the synthesis of enol carbonates was adopted and predominant O-acylation was achieved. In this case, the enolate 2.30 was obtained by deprotonation of acetophenone with the H\(^+\) arpoon lithium amide base LiTMP (2.29). The crucial point in this case is that the liberated amine should not be more reactive towards the carbamoyl chloride than the enolate. Olofson and coworkers found out that indeed HTMP did not compete in the reaction with the acylation reagent. LiTMP (2.29) was conveniently prepared at room temperature by reacting MeLi with HTMP in THF. The enolate 2.30 was formed at -70 °C. After warming the reaction mixture to room temperature and the addition of HMPA, which promoted preferential O-acylation, the enolate 2.30 was reacted with diisopropyl carbamoyl chloride. During the work-up, HTMP and HMPA were efficiently removed by extraction with a pH 4 aqueous citrate solution and the product 2.31 was obtained with an improved 49% yield, compared to 2.21 and 2.28. As no evident side products were detected, the modest yield was mainly attributed to the lower reactivity of the carbamoyl chloride compared to chloroformates; an observation also reported by Olofson and coworkers.

Hoppe and coworkers described an alternative synthesis of 1-aryl-vinyl N,N-diisopropyl carbamates (Scheme 2.17). Aryl ketones were reacted with N,N-diisopropyl carbamoyl chloride in the presence of pyridine at temperatures ≥95 °C for 6 to 9 days (34-73% yields). Although operationally simple, the reaction times are rather long and the scope is not wide.

**Scheme 2.17**  Alternative synthesis of 1-aryl-vinyl N,N-diisopropyl carbamates

### 2.7 Vinyl carbamates as bidentate substrates

As previously mentioned, the importance of the use of chelating substrates in Rh-catalyzed asymmetric hydrogenation is well known. Therefore, the ability of the substrate to coordinate efficiently to the metal center does influence the outcome of the reaction in terms of both reactivity and enantioselectivity. The spectroscopic data depicted in Scheme 2.18 furnish a possible comparison between vinyl acetate 2.5a and vinyl carbamate 2.21. The latter was expected to have a more electron-
rich carbonyl moiety. Indeed, the carbonyl signal of 2.21 appeared at higher field in the $^{13}$C-NMR compared to 2.5a indicating that it is more shielded. These values were compared with those of the equivalent N-acyl 1-phenyl enamide (2.32) reported by Burk and coworkers.29

![Scheme 2.18](image)

Scheme 2.18 $^{13}$C-NMR evidence for electronic differences between 1-phenyl-vinyl acetate (2.5a), 1-phenyl-vinyl N,N-dimethyl carbamate (2.21) and N-acyl 1-phenyl enamide (2.32).

It was striking to notice that the carbonyl group of the vinyl acetate 2.5a was the most similar to the carbonyl of the enamide 2.32 (Scheme 2.18, 169.0 vs 168.5 ppm). On the other hand, the value of the $^{13}$C-NMR for the $\alpha$-carbon turned out to be similar between vinyl acetate 2.5a and carbamate 2.21, but completely different from the same carbon of the enamide 2.32 (153.2 vs 139.9 ppm). Moreover, there is no significant influence on the $\beta$-carbon, which has a similar value in all three compounds (101.4-102.0 ppm). As expected, vinyl acetate 2.5a turns out to have the most electron-poor carbonyl group and double bond among the molecules considered. On the other side, enamide 2.32 has a more electron-rich $\alpha$-carbon on the double bond, which should confer to the molecule better binding properties. Conversely, vinyl carbamate 2.21 has a more electron-rich carbonyl moiety, due to the presence of the amino group, which could counterbalance the in principal less efficient binding of the double bond to the metal center, compared to the enamide 2.32.
2.8 Hydrogenation of 1-phenyl-vinyl N,N-dialkyl carbamates

At first, 1-phenyl-vinyl N,N-methyl carbamate (2.21) was tested in the Rh-catalyzed asymmetric hydrogenation. In view of the strong influence of the phosphoramidite ligand structure observed in the hydrogenation of aromatic enol acetates 2.5a-c on both activity and enantioselectivity, more ligands were tested in this part of the investigation (Scheme 2.19).

![Scheme 2.19 Monodentate phosphoramidites used in this study](image)

During this first screening 2 mol% of catalyst loading was used and CH$_2$Cl$_2$ was chosen as the solvent. The results are shown in Table 2.6.

Hydrogenation of 2.21 confirmed our assumptions, as evidenced by an increase of enantioselectivity from 90% for 2.6a to 94% ee for 2.22 using ligand A3 (Table 2.6, entry 2). Very good activities were obtained in almost all cases, except when a sterically demanding amine (A9, entry 8) or BINOL moiety (C3, entry 10) were used. The variety of enantioselectivities obtained demonstrates the influence of the ligand structural features. Other heterocyclic ring sizes in the ligand (A5 and A8) resulted in poorer enantioselectivities compared to A3. Changing the backbone of the ligand from BINOL (A3) to octahydro-BINOL (B3) produced no change in the enantioselectivity as 94% ee was achieved in both cases (entries 2 and 9). Under these conditions, in one occasion the reaction was performed at -20 °C (entry 11) affording 2.22 with an increased 97% ee but incomplete conversion. Nevertheless, the activity could be regained by increasing the hydrogen pressure, as this was already demonstrated to have no negative effect on the enantioselectivity (Table 2.3).
Table 2.6  Asymmetric hydrogenation of 1-phenyl-vinyl N,N-dimethyl carbamate

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand</th>
<th>conversion&lt;sup&gt;a,b&lt;/sup&gt; (%)</th>
<th>ee&lt;sup&gt;c,d&lt;/sup&gt; (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>A1</td>
<td>100</td>
<td>19 (R)</td>
</tr>
<tr>
<td>2</td>
<td>A3</td>
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<td>A4</td>
<td>100</td>
<td>93 (R)</td>
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</tr>
<tr>
<td>5</td>
<td>A6</td>
<td>100</td>
<td>64 (R)</td>
</tr>
<tr>
<td>6</td>
<td>A7</td>
<td>6</td>
<td>22 (R)</td>
</tr>
<tr>
<td>7</td>
<td>A8</td>
<td>100</td>
<td>76 (R)</td>
</tr>
<tr>
<td>8</td>
<td>A9</td>
<td>3</td>
<td>92 (R)</td>
</tr>
<tr>
<td>9</td>
<td>B3</td>
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<td>C3</td>
<td>77</td>
<td>15 (R)</td>
</tr>
<tr>
<td>11</td>
<td>A3</td>
<td>69&lt;sup&gt;e&lt;/sup&gt;</td>
<td>97 (R)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Reactions performed in 4 mL of solvent with 0.2 mmol of substrate and 2 mol% of catalyst at rt for 16 h. <sup>b</sup>Conversions determined by <sup>1</sup>H NMR or GC. <sup>c</sup>ee’s determined by chiral GC. <sup>d</sup>In all cases, the (S)-enantiomer of the ligand was used. <sup>e</sup>Reaction performed at -20 °C.

In view of the superior performance of ligands A3 and B3, they were selected as the ligands of choice for further studies. Table 2.7 shows the results obtained in the hydrogenation of 1-phenyl-vinyl N,N-dialkyl carbamates 2.28 and 2.31 varying the substitution pattern on the nitrogen.

A small increase in ee from 94% to 96% was noted in the hydrogenation of the N,N-diethyl carbamate 2.28, with both ligands A3 and B3 (entries 3 and 5). An excellent 98% ee (entry 4) was also obtained by decreasing the temperature to -20 °C and, as mentioned before, full conversion was achieved using an higher hydrogen pressure. On the other hand, no further improvement was achieved using substrate 2.31. It should be emphasized that the catalyst loading for this set of reactions was reduced to 1 mol%, without affecting reactivity or enantioselectivities (entry 1). A closer look at the reaction rate revealed an efficient catalytic system and a substantial difference between ligands A3 and B3, as the reactions were found to be finished in around 4 h and 2 h, respectively.30
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Table 2.7  Asymmetric hydrogenation of 1-phenyl-vinyl N,N-dialkyl carbamates

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>product&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ligand</th>
<th>ee&lt;sup&gt;a,b&lt;/sup&gt; (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.21&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.22</td>
<td>A3</td>
<td>94 (R)</td>
</tr>
<tr>
<td>2</td>
<td>2.21&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.22</td>
<td>A3&lt;sup&gt;b&lt;/sup&gt;</td>
<td>95 (R)</td>
</tr>
<tr>
<td>3</td>
<td>2.28&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.33</td>
<td>A3</td>
<td>96 (R)</td>
</tr>
<tr>
<td>4</td>
<td>2.28&lt;sup&gt;f&lt;/sup&gt;</td>
<td>2.33</td>
<td>A3</td>
<td>98 (R)</td>
</tr>
<tr>
<td>5</td>
<td>2.28&lt;sup&gt;g&lt;/sup&gt;</td>
<td>2.33</td>
<td>B3</td>
<td>96 (R)</td>
</tr>
<tr>
<td>6</td>
<td>2.31&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2.34</td>
<td>A3</td>
<td>95 (R)</td>
</tr>
</tbody>
</table>

<sup>a</sup>Reactions performed in 4 mL of solvent with 0.2 mmol of substrate and 1 mol% of catalyst at rt for 16 h. <sup>b</sup>All reactions went to full conversion. *ee’s were determined by chiral GC. <sup>c</sup>In all cases, the (S)-enantiomer of the ligand was used. <sup>d</sup>Reaction complete after 4 h. <sup>e</sup>Reaction carried out at -20 °C and 20 bar H₂. <sup>f</sup>Reaction complete after 2 h. <sup>g</sup>Reaction performed in DCE.

This investigation confirmed our assumption that vinyl carbamates 2.20 are better substrates than vinyl acetates 2.5 (90% ee vs 96% ee). Changes in the substituents on the amine moiety did not seem to have a very significant influence in terms of sterics. It remains to be seen what would have happened with different substitution patterns, as for example more electron rich substituents on the amino group. Nevertheless, it was convenient at this stage to learn that the N,N-diisopropyl carbamoyl group was not better than the others, as N,N-diisopropyl carbamoyl chloride is more expensive.

2.9 Expanding the scope of the use of vinyl carbamates

In view of these excellent results, we decided to expand the substrate scope further. Nevertheless, it became immediately clear that also a new synthetic approach was necessary.

A complex reaction mixture and no product were obtained when using both the previously adopted methods A and B (Scheme 2.20) for the preparation of 1-p-NO₂-phenyl-vinyl N,N-dimethyl carbamate (2.36). A modified version of method B
was also attempted. In this case the enolate was directly obtained with NaH but a mixture of THF and HMPA was used as solvent (method C). Also from this approach, only a complex mixture was obtained in which the product was not present. Clearly, the reaction conditions were not selective for the carbonyl group anymore. An involvement of the para-nitro functionality of ketone 2.35 seemed to be a reasonable explanation for the complex reaction mixture.

![Scheme 2.20 Attempts for the synthesis of 1-p-NO₂-phenyl-vinyl N,N-dimethyl carbamate (2.36)](image)

The pathway proposed by Hoppe (Scheme 2.17) was also taken into consideration, for the synthesis of 1-p-NO₂-phenyl-vinyl N,N-diethyl carbamate 2.37 (Scheme 2.21). On this occasion, after one week at 95 °C, almost no product was observed. The same methodology was also employed attempting the synthesis of the alkyl vinyl carbamate 2.38. Again, after 4 days of reaction at 95 °C, no conversion was observed.

![Scheme 2.21 Attempts for the synthesis of 1-p-NO₂-phenyl-vinyl N,N-diethyl carbamate 2.37 and n-butyl-vinyl N,N-dimethyl carbamate 2.38](image)
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The methodology proposed by Olofson and coworkers\textsuperscript{26} was also adopted for the synthesis of dienyl carbamates 2.39 and 2.40 from the corresponding ketones (Scheme 2.22). The products were isolated in modest yields from complex reaction mixtures, showing a possible involvement of the additional double bond. Nevertheless, these compounds were of particular interest as hydrogenation substrates, as they represented the equivalent of the dienyl acetates 2.12a-b used by Boaz with Rh-DuPHOS (L3) as chiral catalyst (Scheme 2.5).\textsuperscript{9}

\[
\begin{align*}
\text{O}_\text{R} & \quad \text{O} \\
\text{N} & \quad \text{O} \\
\text{N} & \quad \text{O}
\end{align*}
\]

Scheme 2.22 Synthesis of dienyl carbamates 2.39 and 2.40.

The limitations of the syntheses used, stimulated us to look for different approaches that would allow the preparation of a wider range of compounds under milder and more selective conditions. Searching in the literature, we came across a very interesting methodology described by Snieckus and coworkers involving the regiospecific α-lithiation of the simple vinyl carbamate 2.41 (Scheme 2.23).\textsuperscript{31}

\[
\begin{align*}
\text{R'}X & \quad \text{Li} \\
\text{N} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{N} & \quad \text{O} \\
\text{Li} & \quad \text{OCONEt}_2
\end{align*}
\]

Scheme 2.23 Enol carbamates 2.43 by regiospecific α-lithiation of enol carbamate 2.41

The α-metalated vinyl carbamate 2.42 constitutes a readily available and stable acyl anion equivalent in a very simple form, which, in principal, can be trapped with a variety of electrophiles, providing a general synthetic pathway. This approach is based on the principal of umpolung or reversal of polarity, first introduced by Corey and Seebach,\textsuperscript{32} which found numerous synthetic applications.\textsuperscript{33}

The synthon 2.41 was prepared by trapping the corresponding lithium enolate 2.44, formed from the fragmentation of THF mediated by n-BuLi at room temperature,
with $N,N$-diethyl carbamoyl chloride in the presence of HMPA, as described in Scheme 2.24.

![Scheme 2.24 Synthesis of vinyl N,N-diethylcarbamate 2.41](image)

The fragmentation, initiated by the deprotonation of THF, is the result of a symmetry-allowed cycloreversion$^{34}$ as reported by Bates and coworkers.$^{35}$ Cleavage of ethers using organoalkali metal compounds has been reported in the literature.$^{36}$ Moreover, this side reaction has been the object of NMR studies in view of possible synthetic applications of the metal enolates formed.$^{35,37}$ In a report by Jung and Blum, the lithium enolate of acetaldehyde 2.44 was obtained on a preparative scale and used in O-acylation and O-silylation reactions.$^{38}$ Modifications of these literature procedures allowed the preparation on a multigram scale of 2.41 isolated in 65% yield by silica gel flash chromatography. The initial use of 3 equivalents of $N,N$-diethyl carbamoyl chloride afforded a conversion of 78%. However, the excess of reagent still present complicated the purification of the product, resulting in a much lower isolated yield of the pure product (25-40%). Eventually, the use of 1.1 equivalents of carbamoyl chloride seemed to be a good compromise between reactivity and purification issues. Alternatively, the product could be isolated by distillation under reduced pressure but again the product was contaminated by the presence of residual carbamoyl chloride, so column chromatography was preferred.$^{39}$

According to the literature procedure, vinyl carbamate 2.41 was lithiated in the $\alpha$-position at -78 °C using sec-BuLi in the presence of TMEDA in THF, following a reverse addition protocol (Scheme 2.23).$^{51}$ The reaction of electrophiles with the resulting species 2.42 would then lead to the desired $\alpha$-substituted vinyl carbamates 2.43 with alkyl halides serving as effective reaction partners.

This seemed appealing, as we were interested in the possibility of preparing in a regioselective manner terminal alkyl vinyl carbamates to test in the asymmetric
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hydrogenation reaction. Nevertheless, in our hands following the reported protocol, reaction with n-butyl iodide or benzyl bromide did not afford the expected products 2.45 and 2.46 and the starting material 2.41 was instead recovered (Scheme 2.25). Using the more reactive TMSCl, the expected product 2.47 was obtained in 57% isolated yield.\textsuperscript{40} This at least guaranteed that the α-lithio vinyl carbamate 2.42 was indeed formed.

![Scheme 2.25](image)

**Scheme 2.25 Synthesis of N,N-dimethyl vinyl carbamates 2.45-2.47**

The procedure implied that the electrophile was added at -78 °C and maintained at this temperature for one hour. Subsequently the reaction mixture was allowed to warm to room temperature, where it was quenched after 15 minutes with ammonium chloride. A number of attempts was made in order to increase the reactivity by changing some of the reaction conditions. For example, the temperature at which n-butyl iodide was added was increased to -60 °C, or the reaction mixture was maintained at -78 °C for a couple of hours. Alternatively, after reaching room temperature, the reaction mixture was stirred for longer periods or more n-butyl iodide was used. Unfortunately, none of these attempts led to any improvement. Moreover, there was the risk that higher temperatures might cause instability of the lithium intermediate 2.42.

Transmetallation to α-cuprate vinyl carbamates (2.48) seemed at this point to be a possible solution as it would allow temperatures more suitable for the alkylation reducing the risk of degradation. The procedure adopted is described in Scheme 2.26. Percy and coworkers used this approach in order to increase the reactivity of the α-lithio fluoro-vinyl carbamate equivalent of 2.42, which resulted to be much less reactive than 2.42.\textsuperscript{41}
The copper salt CuI·2LiCl used for the transmetallation was prepared according to a procedure described by Reetz and coworkers and has the advantage of being soluble in THF. Upon addition of the copper salt, as a 1M THF solution at -78 °C, to the α-lithio vinyl carbamate 2.42, the reaction mixture was stirred for 1 hour before raising the temperature to 0 °C. Upon addition of the electrophile, stirring was continued for two hours at 0 °C and overnight at room temperature. In this way, vinyl carbamate 2.46 was isolated in 40% yield, but only traces of product 2.45 were detected in the crude mixture by 1H-NMR and TLC. The α-cupro vinyl carbamate 2.48 did not show better reactivity toward simple alkyl electrophiles. It was decided to abandon this synthetic pathway without trying any optimization of the reaction conditions.

As mentioned before (see page 50) HMPA is known to enhance the reactivity of enolates in THF by weakening the coordination between the metal and the enolate itself. The aim was to achieve better reactivity and regioselectivity during O-acylation. It was decided to use HMPA as an additive also on this occasion in order to increase the reactivity of 2.42 by solvation of the metal (Scheme 2.27).

The α-lithio vinyl carbamate 2.42 was prepared as described before and n-butyl iodide was added at -78 °C followed by HMPA. Immediately a change of color was noticed. The temperature was increased to room temperature and the reaction was quenched after 2 hours. This modified protocol proved to be very efficient as vinyl carbamate 2.45 was finally isolated in 75% yield. The reaction was also performed using benzyl bromide yielding 2.46 with an improved 52% yield.

Snieckus and coworkers reported that the same synthon 2.41 could also be used for the preparation of aryl or heteroaryl derivatives. The α-lithio carbamate 2.42
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was in this case transmetallated with ZnBr$_2$. The α-Zn species 2.49 obtained was used in Negishi cross coupling reactions (Scheme 2.28). Instead of the reported PdCl$_2$(dppt), the already available PdCl$_2$(PPh$_3$)$_2$ was used as catalyst during the reaction. This allowed the preparation of the p-NO$_2$-phenyl-vinyl carbamate 2.37, which could not be prepared before. Moreover, using these reaction conditions dienyl carbamate 2.39 was obtained with an improved 62% yield.

\[ \text{ZnBr}_2 \xrightarrow{\text{THF}} \text{BrZn} \]

\[ \text{PdCl}_2(\text{PPh}_3)_2 \xrightarrow{\text{RX}} \]

\[ \text{RX}=\text{p-NO}_2\text{-PhBr}, 41\% \text{ yield} \]

\[ \text{RX}=\text{trans-1-heptenyl iodide}, 62\% \text{ yield} \]

Scheme 2.28 Synthesis of p-NO$_2$-phenyl (2.37) and alkenyl (2.39) N,N-diethyl vinyl carbamates

The trans-1-heptenyl iodide (2.53) used as starting material for the preparation of 2.39 was not commercially available. However, it was conveniently synthesized by stereospecific and regioselective conversion of 1-heptyne (2.50) via hydroboration as described in Scheme 2.29.\textsuperscript{45}

\[ \text{C}_9\text{H}_{11}\text{BH} \xrightarrow{1.\Delta 2.\text{H}_2\text{O}} \text{C}_9\text{H}_{11}\text{BOH} \xrightarrow{1.\text{NaOH} 2.\text{I}_2} \text{C}_9\text{H}_{11}\text{BI} \]

Scheme 2.29 Synthesis of trans-1-heptenyl iodide (2.53) via hydroboration

The catechol ester of trans-1-heptenylboronic acid 2.52 was exclusively obtained from the reaction between catechol borane (2.51) and 1-heptyne (2.50) at 70 °C. The ester was subsequently hydrolyzed to the trans-1-heptenylboronic acid (2.52). After isolation, boronic acid 2.52 was reacted first with an aqueous solution of NaOH, after which an ethereal solution of I$_2$ was added dropwise. The desired product 2.53 was obtained in 56% yield after purification by distillation. The sequential steps in this second part of the synthesis were particularly important, as too fast addition of I$_2$ yielded in a first attempt a mixture of cis and trans products.\textsuperscript{46}
In spite of the problems initially encountered, α-lithio vinyl carbamate 2.42 proved to be a general and versatile synthon for a mild and regioselective preparation of differently α-substituted vinyl N,N-diethyl carbamates.

The reactions involving the use of vinyl carbamate 2.41 (Scheme 2.27 and Scheme 2.28) are mild, selective and the crude mixtures resulting are rather uncomplicated.

2.10 Hydrogenation of a range of α-substituted vinyl N,N-diethyl carbamates

The α-substituted vinyl N,N-diethyl carbamates prepared (Scheme 2.30) were subsequently tested as substrates in the Rh-catalyzed asymmetric hydrogenation. Once more, the best ligands (A3, B3) and solvent (CH2Cl2) were used and the results are depicted in Table 2.8.

![Scheme 2.30 α-Substituted vinyl N,N-diethyl carbamates used in Rh-catalyzed asymmetric hydrogenation](image)

An excellent 98% ee (entry 1) was obtained for substrate 2.37, confirming also for enol carbamates the importance of an electron-withdrawing group on the aromatic moiety. Moreover, this substituent had a beneficial influence also on the activity, as the reaction was finished after around 1 h. According to Burk, the presence of electron-withdrawing groups enhances metal olefin binding, resulting in higher rates and enantioselectivities.8j
Table 2.8  Hydrogenation of α-substituted vinyl N,N-diethyl carbamates

<table>
<thead>
<tr>
<th>entry</th>
<th>substrate</th>
<th>product</th>
<th>ligand</th>
<th>H2 (bar)</th>
<th>ee (%)</th>
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</tr>
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<td>2.55</td>
<td>A3</td>
<td>5°</td>
<td>64 (S)</td>
</tr>
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<td>2.59</td>
<td>B3</td>
<td>10</td>
<td>77 (R)</td>
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</table>

Reactions performed in 4 mL of solvent with 0.2 mmol of substrate and 1 mol% of catalyst at rt for 16 h. Conversions determined by 1H-NMR or GC, all reactions went to completion. ee’s were determined by chiral GC. In all cases, the (S)-enantiomer of the ligand was used. Conversion 41%. The absolute configuration has not been established.

As shown for substrate 2.46 (entry 5), the presence of a benzyl group causes a decrease in enantioselectivity (73% ee) although full conversion was achieved with 5 bar H2 (in approximately 10 h) using the catalyst based on ligand A3. Using higher hydrogen pressure afforded the product 2.56 with identical enantioselectivity but in approximately 6 h (entry 6). When the substituent is an alkyl group (substrate 2.45), a further decrease in enantioselectivity (63% ee, entry 3) was observed and a higher pressure was necessary in order to reach full conversion. It was pleasing to see an increase both in terms of enantioselectivity (69% ee) and reactivity (only 10 bar H2 were used) for this substrate when ligand B3 was employed (entry 4). The results using substrates 2.45 and 2.46 are comparable with those obtained by using DuPHOS (L3) on similar enol acetates (2.10a-b, Scheme 2.5). Interestingly the sterically hindered substrate 2.47 could also be hydrogenated to full conversion (entry 7) although the enantioselectivity was modest. To our surprise, an excellent 97% ee was achieved for the 2-dienyl substrate 2.39 (entry 8), and only 10 bar H2.
was necessary to achieve complete conversion to the product 2.58. A similar phenomenon was previously observed by using DuPHOS (L3) on a similar enol acetate (2.12a, Scheme 2.5). On the other hand, lower enantioselectivity was observed for the 2-dienyl carbamate 2.40 (entries 10 and 11). It should be mentioned that in both cases the catalytic system showed very good selectivity as the hydrogenation proceeded leaving the extra internal double bond intact. In one case (entry 9), increasing further the hydrogen pressure seemed to make the reaction slightly less regioselective, as a small amount (< 5%) of over hydrogenated product was also observed.

2.11 Conclusions and outlook

In conclusion, we have shown that monodentate phosphoramidites, in particular PipPhos (A3) and its octahydro analogue (B3), are excellent ligands for the rhodium-catalyzed asymmetric hydrogenation of aromatic enol acetates, aromatic enol carbamates and 2-dienyl carbamates with excellent enantioselectivities up to 98%. Fast reactions were achieved (TOF up to 100 h⁻¹, 5 bar H₂), making the combination of enol carbamates and monodentate phosphoramidites very competitive compared to the existing systems.

High enantioselectivities with aliphatic vinyl carbamates, such as 2.45, 2.46, remain an interesting challenge. The results even if not extremely exciting (69% and 73% ee) are comparable to what was obtained using Duphos (64% and 77% ee) and the catalyst appeared to be rather active as full conversion was achieved using 5 and 10 bar H₂ pressure, respectively. Also Reetz and coworkers reported moderate results (up to 65% ee) in the hydrogenation of vinyl carboxylate 2.60 using simple monodentate phosphite ligands such as L8 without any match/mismatch combination provided by the carbohydrate backbone (Scheme 2.31), demonstrating that the structure of the ligand is extremely important.

\[
\text{Scheme 2.31 } \text{Hydrogenation of vinyl carboxylate 2.60 with chiral phosphite L8}
\]

Before the carbohydrate based ligands, described by Reetz (Scheme 2.6), were employed the best result reported was obtained by direct hydrogenation of 2-hexanone (2.25) using Rh-PennPhos catalyst and affording 2.62 with 75% ee (Scheme 2.32). Nevertheless, the system was rather slow, as 48 hours and 30 bar hydrogen pressure were necessary to reach 96% conversion.
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Scheme 2.32  Asymmetric hydrogenation of 2-hexanone (2.25)

Very interestingly, the hydrogenation of 2-dienyl carbamate 2.39 afforded the product 2.58 with an excellent 97% ee. The regioselectivity would suggest, as depicted in Scheme 2.33, a distinct preferential coordination of the terminal double bond and the carbamoyl group to the metal center (2.63) compared to the other possible complexes 2.64 and 2.65.

Scheme 2.33  Possible coordination between Rh and dienyl carbamate 2.39

Furthermore, the high enantioselectivity would also suggest that the poorer results obtained with 2.45 might be mainly the result of steric rather than electronic effects, especially considering that also for 2.59 a lower enantiomeric excess was achieved (77% ee). This would suggest that the flexibility of the alkyl chain could be detrimental for the enantioselectivity. In this respect, it would be interesting to see which results the use of the cis-dienyl equivalent of 2.39 would provide. Very good enantioselectivities with these dienol substrates were reported not only by Boaz (Scheme 2.5) and by us, but were found also in the hydrogenation of the corresponding α,β-unsaturated ketones using ruthenium catalysts (Scheme 2.34).48
Chapter 2

Scheme 2.34  Hydrogenation of α,β-unsaturated ketones to allyl alcohols

It seems likely that the substrate scope could be expanded substantially, by screening a wider variation of ligands and even combination of different ligands.\(\text{5,49}\) Phosphoramidites being monodentate ligands and having a modular structure are perfect candidates for a combinatorial approach. The dramatic influence of the chiral ligand was already underlined by the results provided by MonoPhos\(\text{TM} (A1)\) and PipPhos\( (A3)\) in the hydrogenation of both 2.5a and 2.21. In this respect, the chair conformation of the piperidine ring might provide a more defined or constrained chiral environment that suits this class of substrates more than others previously tested. For example, it has already been observed by\(^{31}\text{P}-\text{NMR}\) studies that by mixing Rh(COD)\(_2\)BF\(_4\) with 2 equivalents of MonoPhos\(\text{TM} (A1)\) more than one complex can be observed containing different rhodium to ligand ratios.\(\text{13}\)

The assumption that vinyl carbamates should be better substrates than vinyl acetates was confirmed by the results obtained for 2.5a (90% ee) and 2.31 (96% ee). Moreover, the use of a carbamate as stereo-directing group allowed the regioselective preparation of a diverse number of substrates starting from the very useful and simple compound 2.41. The versatility of the carbamate moiety could be further exploited due to the configurational stability in apolar solvents of the related lithium derivatives, an example of which is reported in Scheme 2.35.\(\text{50}\)
Enantioselective Rh-Catalyzed Hydrogenation of Enol Acetates and Enol Carbamates with Monodentate Phosphoramidites

Scheme 2.35  Tertiary chiral esters from chiral hydrogenation product 2.34

As demonstrated by Hoppe and coworkers,\textsuperscript{51} tertiary lithium intermediate 2.71 derived from benzyl carbamate 2.34 undergoes electrophile-dependent stereo-divergent substitutions, affording tertiary chiral esters 2.72 and 2.73. Furthermore, the substitution with Me\textsubscript{3}SnCl proceeds with inversion to provide access to the other enantiomer of the products.\textsuperscript{52}

Moreover, optically active allylic carbamates 2.58 and 2.59 could be used for further transformations involving the remaining unsaturation. In a generic sense, the chiral allylic alcohol or its carbamate derivative might serve as stereo-directing and possible metal binding site for all kind of reactions involving a double bond (Heck reaction, hydroformylation, epoxidation, etc.).\textsuperscript{53} An intriguing idea would be to employ the enantiomerically enriched allylic carbamates in regioselective and enantiospecific Rh-catalyzed allylic substitutions reactions using the carbamate as leaving group.\textsuperscript{54,55}

Scheme 2.36  Regioselective, enantiospecific Rh-catalyzed allylic substitutions reactions

Finally, chiral allylic alcohol derivatives can undergo selective Claisen rearrangement via a chair transition state affording products with an extra stereogenic center, which still retain a double bond (Scheme 2.37).\textsuperscript{56}

Scheme 2.37  Claisen rearrangement of chiral allylic alcohol derivatives
2.12 Experimental section

General remarks
All reactions were performed in a dry nitrogen atmosphere using standard techniques. Solvents were reagent grade, dried and distilled before use following standard procedures.57

$^1$H-NMR and $^{13}$C-NMR spectra were recorded at room temperature in CDCl$_3$ on a Varian VXR300 (300 MHz) spectrometer. Chemical shifts were determined relative to the residual solvent peaks (CDCl$_3$, $\delta = 7.26$ ppm for proton, $\delta = 77$ ppm for carbon). Data are reported as follows: chemical shift, multiplicity ($s = $ singlet, $d = $ doublet, $t = $ triplet, $q = $ quartet, $br = $ broad, $m = $ multiplet), coupling constants (Hz) and integration. Mass spectra were recorded on an AEI-MS-902 mass spectrometer. Melting points were measured on a Büchi B-545 melting point apparatus and are uncorrected. Optical rotations were measured on a Schmidt-Haensch Polartronic MH8 polarimeter. Enantiomeric excesses and conversions were determined by capillary GC analysis on a HP 6890 or 5890 gas chromatograph equipped with a flame ionization detector. All the monodentate phosphoramidite ligands have been previously described and are generally available in our laboratories.58

1-(3,5-Dioxa-4-phospha-cyclohepta[2,1-a;3,4-a’]dininaphthalen-4-yl)-piperidine (S)-A3:

(S)-Bis-$\beta$-naphthol (5 g, 17.5 mmol) in PCl$_3$ (20 mL) was heated under reflux for 8 h. Excess of PCl$_3$ was removed by distillation under reduced pressure (20 mbar). The residual solid was subjected to azeotropic distillation with toluene (2 x 10 mL) and dried in vacuum. The resulting yellowish foam was dissolved in toluene (25 mL) and added dropwise at 0 °C to a solution of triethylamine (5.3 mL, 38.5 mmol, 2.2 eq) and distilled piperidine (1.9 mL, 19.3 mmol, 1.1 eq) in dry THF (37.5 mL). The reaction mixture was then allowed to warm to room temperature and it was stirred overnight. The reaction mixture was diluted with dry diethyl ether (125 mL), filtered over a plug of silica and washed with diethyl ether (125 mL). The solvent was removed under reduced pressure and the crude mixture was purified by silica gel flash chromatography (heptane / ethyl acetate 8:1) affording the desired product as a white solid (89%).

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 7.87-8.03 (m, 4H), 7.52-7.15 (m, 8H), 3.04-2.81 (m, 4H), 1.58-1.26 (m, 6H). $^{13}$C-NMR (50 MHz, CDCl$_3$) $\delta$ 150.0 (s), 149.6 (s), 132.8 (s), 132.6 (s), 131.3 (s), 130.7 (s), 130.2 (d), 129.7 (d), 128.3 (d), 128.2 (d), 127.0 (d), 126.9 (d), 126.0 (d, 2C), 124.7 (d), 124.4 (d), 123.9 (s), 122.2 (d), 122.08 (s), 122.05 (d), 45.5 (t), 45.1 (t), 27.0 (t), 26.9 (t), 24.9 (t). $^{31}$P (162 MHz, CDCl$_3$) $\delta$ 145.3.

1-(3,5-Dioxa-4-phospha-cyclohepta[2,1-a;3,4-a’]dininaphthalen-4-yl)-piperidine (S)-A3:
Enantioselective Rh-Catalyzed Hydrogenation of Enol Acetates and Enol Carbamates with Monodentate Phosphoramidites

Synthesis of 1-aryl-vinyl acetates (2.5a-c). Conversion 69%. Purification by vacuum distillation (120 °C, 20 mmHg) afforded the desired product as a colorless liquid (64%). Alternatively, purification by silica gel flash chromatography (pentane / ether, 9:1). ¹H-NMR (300 MHz, CDCl₃) δ 7.52-7.45 (m, 2H), 7.41-7.31 (m, 3H), 5.50 (d, J = 2.2 Hz, 1H), 5.05 (d, J = 2.2 Hz, 1H), 2.29 (s, 3H). ¹³C-NMR (50 MHz, CDCl₃) δ 169.0 (s), 152.7 (s), 133.6 (s), 130.4 (d), 128.9 (d, 2C), 124.7 (d, 2C), 102.0 (t), 20.9 (q).

1-Phenylvinyl acetate (2.5a):

Conversion 69%. Purification by vacuum distillation (120 °C, 20 mmHg) afforded the desired product as a colorless liquid (64%). Alternatively, purification by silica gel flash chromatography (pentane / ether, 9:1). ¹H-NMR (300 MHz, CDCl₃) δ 7.41-7.31 (m, 3H), 5.50 (d, J = 2.2 Hz, 1H), 5.05 (d, J = 2.2 Hz, 1H), 2.29 (s, 3H). ¹³C-NMR (50 MHz, CDCl₃) δ 169.0 (s), 152.7 (s), 133.6 (s), 130.4 (d), 128.9 (d, 2C), 124.7 (d, 2C), 102.0 (t), 20.9 (q).

1-p-Cl-Phenylvinyl acetate (2.5b):

Conversion 70%. Purification by vacuum distillation (150 °C, 20 mmHg) afforded the desired product as a colorless liquid (63%). Alternatively, purification by silica gel flash chromatography (pentane / ether 9:1). ¹H-NMR (400 MHz, CDCl₃) δ 7.39 (dt, J = 8.8, 2.2 Hz, 2H), 7.32 (dt, J = 8.8, 2.2 Hz, 2H), 5.46 (d, J = 2.2 Hz, 1H), 5.05 (d, J = 2.2 Hz, 1H), 2.27 (s, 3H). ¹³C-NMR (50 MHz, CDCl₃) δ 168.9 (s), 151.9 (s), 134.8 (s), 132.8 (s), 128.7 (d, 2C), 126.2 (d, 2C), 102.7 (t), 20.9 (q).

1-p-NO₂-Phenylvinyl acetate (2.5c):

Conversion 62%. Purification by flash column chromatography (heptane / ethyl acetate, 14:1) afforded the desired product as a solid (60%). M.p. = 51.2-52.5 °C (Lit. 51-52 °C). ¹H-NMR (300 MHz, CDCl₃) δ 8.22 (dt, J = 8.8, 2.2 Hz, 2H), 7.62 (dt, J = 8.8, 2.2 Hz, 2H), 5.65 (d, J = 2.6 Hz, 1H), 5.26 (d, J = 2.6 Hz, 1H), 2.31 (s, 3H). ¹³C-NMR (50 MHz, CDCl₃) δ 168.7 (s), 162.8 (s), 151.0 (s), 140.5 (s), 125.7 (d, 2C), 123.9 (d, 2C), 106.1 (t), 20.9 (q).

Synthesis of 1-phenyl-vinyl N,N-dialkyl carbamates:

Method A conversion 69%. Purification by vacuum distillation (120 °C, 20 mmHg) afforded the desired product as a colorless liquid (64%). Alternatively, purification by silica gel flash chromatography (pentane / ether, 9:1). ¹H-NMR (300 MHz, CDCl₃) δ 7.52-7.45 (m, 2H), 7.41-7.31 (m, 3H), 5.50 (d, J = 2.2 Hz, 1H), 5.05 (d, J = 2.2 Hz, 1H), 2.29 (s, 3H). ¹³C-NMR (50 MHz, CDCl₃) δ 169.0 (s), 152.7 (s), 133.6 (s), 130.4 (d), 128.9 (d, 2C), 124.7 (d, 2C), 102.0 (t), 20.9 (q).
was added dropwise in 30 min, while maintaining room temperature. After stirring for an additional 15 min, water (500 mL) was carefully added to the orange solution. The mixture was extracted with heptane (5 x 500 mL) and the combined extracts were washed with brine and dried over magnesium sulfate, followed by removal of the solvent under reduced pressure.

**Method B**

Lithium 2,2,6,6-tetramethyl-piperidine was prepared by adding dropwise MeLi (0.022 mol, ca. 1.6 M in ether) to a solution of 2,2,6,6-tetramethyl-piperidine (3.10 g, 0.022 mol) in THF (20 mL) in order to accommodate the methane evolution. After an additional 10 min, the solution was cooled to -78 °C and the ketone (0.021 mol) in THF (10 mL) was added dropwise over 20 min. Stirring at -78 °C was continued for another 15 min, after which time the enolate solution was warmed to room temperature and diluted with 40 mL of HMPA. At this point the \(N,N\)-dialkyl carbamoyl chloride (3.60 g, 0.022 mol) was added to the reaction mixture. Stirring was continued for two hours. The mixture was poured into 50 mL of aqueous 10% citric acid (buffered to pH 4 with 50% aq. NaOH) and pentane was added (50 mL). After separation, the aqueous phase was extracted with pentane (2 x 50 mL) and the combined organic layers were washed with an aqueous NaHCO₃ solution, water, brine and dried with sodium sulfate, followed by removal of the solvent under reduced pressure.

**Method C**

A solution of the ketone (0.021 mol) in 10 mL of THF (with an additional catalytic amount of MeOH) was added dropwise to a solution of NaH (1.06 g, 0.022 mol, 50% suspension in oil) in 20 mL of THF at 0 °C. After 40 min, the yellow reaction mixture was allowed to reach room temperature and it was stirred for 3 hours, until no further evolution of gas was observed. At this point, a solution of the \(N,N\)-dialkyl carbamoyl chloride (0.032 mol, 1.5 eq.) in 4 mL HMPA was added and the mixture was stirred overnight. After the addition of water (50 mL), the organic layer was separated. The aqueous layer was extracted with ether (3 x 25 mL) and the combined organic layers were washed with water, brine and dried over sodium sulfate. The solvent was then removed under reduced pressure.

1-Phenylvinyl \(N,N\)-methyl carbamate (2.21):

Prepared according to method A. Purification by column chromatography (heptane / ethyl acetate 4:1) afforded the product as a colorless oil (37%). \(^1^H\)-NMR (200 MHz, CDCl₃) \(\delta\) 2.97 (s, 3H), 3.11 (s, 3H), 5.03 (d, \(J = 1.8\) Hz, 1H), 5.42 (d, \(J = 1.8\) Hz, 1H), 7.29-7.50 (m, 5H). \(^{13}\)C-NMR (50 MHz, CDCl₃) \(\delta\) 155.1 (s), 153.2 (s), 134.9 (s), 128.5 (d), 128.3 (d, 2C), 124.7 (d, 2C), 101.4 (t), 36.6 (q), 36.3 (q). MS, \(m/z\) (%): 191 (M⁺, 34%); HRMS for \(C_{11}H_{13}NO_2\), calcd: 191.095, found: 191.095.
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1-Phenylvinyl N,N-diethyl carbamate (2.28):
Prepared according to method A. Purification by flash chromatography (pentane / ether 9:1) afforded the product as a colorless oil (39%). \(^{1}\)H-NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.48 (d, \(J = 6.6\) Hz, 2H), 7.40-7.28 (m, 3H), 5.41 (d, \(J = 1.5\) Hz, 1H), 5.03 (d, \(J = 1.5\) Hz, 1H), 3.45 (q, \(J = 6.6\) Hz, 2H), 3.35 (q, \(J = 6.6\) Hz, 2H), 1.27 (t, \(J = 6.6\) Hz, 3H), 1.17 (t, \(J = 6.6\) Hz, 3H). \(^{13}\)C-NMR (50 MHz, CDCl\(_3\)) \(\delta\) 154.5 (s), 153.4 (s), 135.3 (s), 128.6 (d), 128.4 (d, 2C), 124.9 (d, 2C), 101.4 (t), 42.0 (t), 41.9 (t), 14.3 (q), 13.3 (q). MS, \(m/\text{z}\) (%): 219 (M\(^+\), 24.4%); HRMS for C\(_{13}\)H\(_{17}\)NO\(_2\), calcd: 219.126, found: 219.125.

1-Phenylvinyl N,N-diisopropyl carbamate (2.31):
Prepared according to method B. Purification by flash chromatography (pentane / ether 9:1) afforded the product as a pale yellow solid (49%). M.p. = 60-62 °C. \(^{1}\)H-NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.20-7.60 (m, 5H), 5.40 (d, \(J = 1.8\) Hz, 1H), 4.98 (d, \(J = 1.8\) Hz, 1H), 4.01 (br sept, \(J = 6.6, 6.9\) Hz, 2H), 1.33 (br, 6H), 1.27 (br, 6H). \(^{13}\)C-NMR (50 MHz, CDCl\(_3\)) \(\delta\) 154.6 (s), 153.5 (s), 135.4 (s), 128.5 (d), 128.4 (d), 124.9 (d), 101.3 (t), 46.2 (d, 2C), 21.5 (q, 2C), 20.5 (q, 2C). MS, \(m/\text{z}\) (%): 247 (M\(^+\), 17.4%); HRMS for C\(_{15}\)H\(_{21}\)NO\(_2\), calcd: 247.157, found: 247.158.

Vinyl N,N-diethyl carbamate (2.41):
A solution of n-BuLi (0.032 mol, ca. 1.6 M in hexane) in THF (20 mL) was allowed to stir at room temperature overnight. The solution was then cooled to 0 °C and N,N-diethyl carbamoyl chloride (4.75 g, 0.035 mol) in HMPA (20 mL) was added. The solution was allowed to stir at room temperature overnight, during which the color changed to red. The reaction was quenched with a saturated aqueous solution of ammonium chloride and after extraction with ether (50 ml) the organic layer was washed with water, brine and dried with sodium sulfate. After removal of the solvent under reduced pressure, purification by flash chromatography (pentane / ether 9:1) afforded the product as a colorless liquid (65%). Alternatively, the product was purified by distillation at 25 °C and 1 mmHg (Lit. bp 41 °C at 3 mmHg). \(^{1}\)H-NMR (300 MHz, CDCl\(_3\)) \(\delta\) 7.21 (dd, \(J_{\text{cis}} = 6.3\) Hz, \(J_{\text{trans}} = 13.8\) Hz, 1H), 4.73 (d, \(J_{\text{trans}} = 13.8\) Hz, \(J_{\text{gem}} = 1.5\) Hz, 1H), 4.39 (d, \(J_{\text{gem}} = 1.5\) Hz, \(J_{\text{cis}} = 6.3\) Hz, 1H), 3.29 (q, \(J = 7.2\) Hz, 4H), 1.13 (t, \(J = 7.2\) Hz, 6H). \(^{13}\)C-NMR (50 MHz, CDCl\(_3\)) \(\delta\) 143.5 (s), 140.1 (d), 92.3 (t), 39.5 (t), 38.9 (t), 11.6 (q), 10.7 (q). MS, \(m/\text{z}\) (%): 143 (M\(^+\), 18.9%); HRMS for C\(_7\)H\(_{13}\)NO\(_2\), calcd: 143.095, found: 143.094.

Synthesis of \(\alpha\)-substituted vinyl N,N-diethyl carbamates via transmetallation with Cul2LiCl:
A solution of vinyl N,N-diethyl carbamate 2.41 (0.40 g, 2.79 mmol) in THF (8 mL) was added dropwise to a THF solution (18 mL) of sec-BuLi (2.92 mmol, ca. 1.3 M in hexane) and TMEDA (0.45 mL, 2.98 mmol) at -78 °C. The reaction mixture was
allowed to stir at -78 °C for 1 h. In the mean time LiCl (336 mg, 8 mmol, flamed dried under vacuum and stored over P₂O₅) and Cul (760 mg, 4 mmol) were stirred in THF (4 mL, 1M) until a complete clear solution was obtained (10-15 min). Part of this solution (2.95 mL, 2.95 mmol) was added to the reaction mixture that turned from colorless to bright yellow. The solution was allowed to reach 0 °C over a period of 15 min., after which time RX was added. After stirring at 0 °C for additional two hours, the temperature was increased to room temperature and stirring was continued overnight. The solution was subsequently quenched with a saturated aqueous solution of ammonium chloride (20 mL), extracted with ether (3 x 50 mL) and the combined organic layers were washed with water, brine, dried over sodium sulfate and the solvent was removed under reduced pressure.

Table 2.9 General procedures for synthesis of substrates α-substituted vinyl N,N-diethyl carbamates:

<table>
<thead>
<tr>
<th>RX</th>
<th>Procedure</th>
<th>Product</th>
</tr>
</thead>
<tbody>
<tr>
<td>O₂N-Br</td>
<td>Procedure E</td>
<td>2.37</td>
</tr>
<tr>
<td>I</td>
<td>Procedure D</td>
<td>2.45</td>
</tr>
<tr>
<td>Br</td>
<td>Procedure D</td>
<td>2.46</td>
</tr>
<tr>
<td>SiCl</td>
<td>Procedure D</td>
<td>2.47</td>
</tr>
<tr>
<td>No HMPA used</td>
<td>Procedure E</td>
<td>2.39</td>
</tr>
</tbody>
</table>

General procedure D
A solution of vinyl N,N-diethyl carbamate 2.41 (0.40 g, 2.79 mmol) in THF (8 mL) was added dropwise to a THF solution (18 mL) of sec-BuLi (2.92 mmol, ca. 1.3 M in hexane) and TMEDA (0.45 mL, 2.98 mmol) at -78 °C. The reaction mixture was allowed to stir at -78 °C for 1 h, after which a solution of RX (3.17 mmol) in HMPA

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(5 mL) was added. After stirring for an additional 15 min. at -78 °C, the solution was allowed to reach room temperature and it was stirred for an additional 2 h. The solution was subsequently quenched with a saturated aqueous solution of ammonium chloride (20 mL), extracted with ether (3 x 50 mL) and the combined organic layers were washed with water, brine and dried over sodium sulfate. After removal of the solvent under reduced pressure, the crude products were purified by flash chromatography (mixtures of pentane / ether) affording the desired compounds.

General procedure E

To a stirred solution of vinyl N,N-diethyl carbamate 2.41 (0.60 g, 4.2 mmol) in THF (20 mL) at -78 °C sec-BuLi (4.6 mmol, ca. 1.3 M in hexane) was added. After 1 h, a solution of ZnBr₂ (1.13 g, 5 mmol, 1.2 eq) in THF (10 mL) was added dropwise. The pale yellow reaction mixture was stirred for an additional 15 min and then allowed to reach room temperature. At this point a solution of [(C₆H₅)₃P]₂PdCl₂ (140 mg, 0.21 mmol, 5 mol%) and RX (6.4 mmol, 1.5 eq) in THF (20 mL) was added; the reaction mixture turned from pale yellow to dark orange and it was allowed to stir at room temperature overnight. The reaction was then quenched with a saturated aqueous solution of ammonium chloride (20 mL), extracted with ether (3 x 50 mL) and the combined organic layers were washed with water, brine and dried over sodium sulfate. Purification by flash chromatography (mixtures of pentane / ether) afforded the desired products.

1-(4-Nitro-phenyl)vinyl N,N-diethylcarbamate (2.37):

yellow oil (41%). ¹H-NMR (300 MHz, CDCl₃) δ 8.19 (d, J = 8.7 Hz, 2H), 7.60 (d, J = 8.7 Hz, 2H), 5.56 (d, J = 2.1 Hz, 1H), 5.23 (d, J = 2.1 Hz, 1H), 3.46 (q, J = 6.9 Hz, 2H), 3.33 (q, J = 6.9 Hz, 2H), 1.27 (t, J = 6.9 Hz, 3H), 1.16 (t, J = 6.9 Hz, 3H). ¹³C-NMR (50 MHz, CDCl₃) δ 153.4 (s), 151.6 (s), 147.7 (s), 141.6 (s), 125.7 (d, 2C), 123.8 (d, 2C), 105.3 (t), 42.3 (t), 41.9 (t), 14.3 (q), 13.3 (q). MS, m/z (%): 264 (M⁺, 4.9%); HRMS for C₁₃H₁₆N₂O₄, calcd: 264.111, found: 264.110.

1-Butylvinyl N,N-diethylcarbamate (2.45):

colorless liquid (75%). ¹H-NMR (300 MHz, CDCl₃) δ 4.69 (s, 1H), 4.64 (s, 1H), 3.30 (br, 4H), 2.24 (t, J = 6.9 Hz, 2H), 1.52-1.27 (m, 4H), 1.15 (t, J = 7.2 Hz, 6H), 0.90 (t, J = 7.2 Hz, 3H). ¹³C-NMR (50 MHz, CDCl₃) δ 156.9 (s), 153.9 (s), 99.9 (t), 41.7 (t, 2C), 33.3 (t), 28.7 (t), 22.1 (t), 14.2 (q), 13.8 (q), 13.4 (q). MS, m/z (%): 199 (M⁺, 7.7%); HRMS for C₁₁H₂₁NO₂, calcd: 199.157, found: 199.157.
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1-Benzylvinyl N,N-diethylcarbamate (2.46):

colorless liquid (52%). 1H-NMR (300 MHz, CDCl₃) δ 7.10-7.32 (m, 5H), 4.77 (s, 1H), 4.60 (s, 1H), 3.56 (s, 2H), 3.24 (br q, J = 6.9 Hz, 2H), 3.07 (br q, J = 6.9 Hz, 2H), 1.09 (t, J = 6.9 Hz, 3H), 0.90 (t, J = 6.9 Hz, 3H). 13C-NMR (50 MHz, CDCl₃) δ 155.8 (s), 152.0 (s), 137.3 (s), 129.2 (d, 2C), 128.3 (d, 2C), 126.5 (d), 101.7 (t), 41.9 (t), 41.6 (t), 40.1(t), 13.8 (q), 13.3 (q). MS, m/z (%): 233 (M⁺, 3.9%); HRMS for C₁₄H₁₉NO₂, calcd: 233.142, found: 233.143.

1-Trimethylsilanylvinyl N,N-diethylcarbamate (2.47):

colorless liquid (57%). 1H-NMR (300 MHz, CDCl₃) δ 5.37 (s, 1H), 5.00 (s, 1H), 3.28 (q, J = 7.2 Hz, 4H), 1.13 (t, J = 7.2 Hz, 6H), 0.15 (s, 9H). 13C-NMR (50 MHz, CDCl₃) δ 164.0 (s), 152.2 (s), 113.1 (t), 41.8 (t, 2C), 14.1 (q), 13.5 (q), -0.1 (q, 3C). MS, m/z (%): 215 (M⁺, 5.4%); HRMS for C₁₀H₂₁NO₂Si, calcd: 215.134, found: 215.135.

Trans-1-heptenyl iodide (2.53):

the catechol ester of 1-heptynylboronic acid was formed by stirring 1-heptyne (4.81 g, 0.05 mol) and catecholborane (6.00 g, 0.05 mol) at 70 °C for 2 h. After this time the mixture was cooled to room temperature and stirred with 50 mL of water for 2 h in order to achieve the hydrolysis of the ester. The resulting mixture was cooled to 0 °C and the white solid, trans-1-hexylboronic acid, was collected by filtration and washed free of the catechol using ice-cold water. The boronic acid was then dissolved in ether (50 mL) and cooled to 0 °C. An aqueous solution of sodium hydroxide (50 mL, 3 N) was then added, followed by the dropwise addition of a solution of I₂ (15.2 g, 0.06 mol) in ether (150 mL). The mixture was allowed to stir at 0 °C for about 30 min. The excess iodine was destroyed with aqueous thiosulfate solution, the ether solution was separated, washed with water and brine, then dried over sodium sulfate. After removing the solvent, Kugelrohr distillation (55 °C at 2 mmHg) afforded the product as a slightly pink liquid (56%). 1H-NMR (300 MHz, CDCl₃) δ 6.51 (dt, J = 14.1, 7.2 Hz, 1H), 5.97 (d, J = 14.1 Hz, 1H), 2.04 (q, J = 7.2 Hz, 2H), 1.45-1.20 (m, 6H), 0.88 (t, J = 6.6 Hz, 3H). 13C-NMR (50 MHz, CDCl₃) δ 146.7 (d), 74.2 (d), 36.0 (t), 31.1 (t), 28.0 (t), 22.4 (t), 13.9 (q).

(E)-1-Methylene-oct-2-enyl N,N-diethylcarbamate (2.39):

colorless liquid (62%). 1H-NMR (300 MHz, CDCl₃) δ 5.98 (d, J = 15.6 Hz, 1H), 5.79 (dt, J = 15.3, 7.2 Hz, 1H), 4.83 (s, 1H), 4.78 (s, 1H), 3.45-3.28 (br, 4H), 2.10 (q, J = 7.2 Hz, 2H), 1.47-1.09 (m, 12H), 0.88 (t, J = 6.9 Hz, 3H). 13C-NMR (50 MHz, CDCl₃) δ 153.6 (s), 152.3 (s), 132.2 (d), 124.9 (d), 102.8 (t), 42.0 (t), 41.6 (t), 32.1, 31.4 (t), 28.6
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(t), 22.5 (t), 14.2 (q), 14.0 (q), 13.3 (q). MS, m/z (%): 239 (M+, 11.0%); HRMS for C_{14}H_{25}NO_{2}, calcd: 239.189, found: 239.190.

(E)-1-Methylene-3-phenyl-allyl N,N-diethylcarbamate (2.40):

Hydrogenation Procedure.
Hydrogenations were performed in an Endeavor™ multireactor autoclave, where the eight reactors are equipped with glass reaction vessels and stirring paddles. In a typical Endeavor run each vessel was charged open to air with Rh(COD)_{2}BF_{4} (2 μmol, 1 mol%), monodentate phosphoramidite (4 μmol, 2 mol%) and substrate (200 μmol). Solvent was added (4 ml), the glass liners were placed in the reactors and the system was closed. After repetitive purging with N_{2} (3 × 2.5 bar) the system was pressurized with hydrogen and the reaction mixtures were stirred at room temperature overnight with 750 rpm. The conversion of the reactions was monitored following H_{2} consumption. The reactions were stopped via release of H_{2} pressure. The resulting mixture was filtered over a short silica column and subjected to conversion (1H-NMR) and enantiomeric excess determination (capillary GC).

Enantiomeric Excess Determinations.
To ensure accurate ee determination, racemic products of 2.56 and 2.57 were prepared by hydrogenation of 2.46 and 2.47 using 10% Pd/C (10%) in MeOH under 1 bar of H_{2} for 16 h. Racemic products of 2.6a-c, 2.22, 2.33, 2.34, 2.54 and 2.55 were prepared by hydrogenation of 2.5a-c, 2.21, 2.28, 2.31, 2.37 and 2.45 using Rh(COD)_{2}BF_{4} and 3 equivalents of PPh_{3} ligand in CH_{2}Cl_{2} under H_{2} pressure. Racemic products of 2.58 and 2.59 were prepared by reduction of the corresponding ketones with NaBH_{4} and carbamoylation of the resulting racemic alcohols. Absolute configurations were determined by comparison with: the GC literature values of identical compounds (2.6a-c), the GC retention time of commercially available enantiopure alcohol 2.74 after carbamate removal (2.22, 2.33, 2.34), the GC retention time of commercially available enantiopure alcohol after carbamoylation (2.55), the HPLC literature value of the corresponding saturated alcohol 2.75 after carbamate removal (2.59), or assigned by analogy through chiral GC elution order (2.54, 2.58). For products 2.56 and 2.57 the absolute configuration was not determined.
Hydrogenation products data.

1-Phenylethyl acetate (2.6a):\(^{74}\)

\[
\text{\(1^H\)-NMR (300 MHz, CDCl}_3\) \(\delta \) 7.37-7.26 (m, 5H), 5.89 (q, \(J = 6.6\) Hz, 1H), 2.08 (s, 3H), 1.54 (d, \(J = 6.6\) Hz, 3H). \(13^C\)-NMR (50 MHz, CDCl}_3\) \(\delta \) 170.3 (s), 141.6 (s), 128.5 (d, 2C), 127.8 (d), 126.1 (d, 2C), 72.3 (d), 22.2 (q), 21.3 (q).
\]

Enantiomeric excess determination: \(\beta\)-DEX 120 column (30 m \(\times \) 0.25 mm \(\times \) 0.125 \(\mu\)m). Init. Temp.: 125 °C, \(T_{\text{det/inlet}}\) = 150 °C, \(t_S = 10.39\) min, \(t_R = 10.92\) min, \(t_{SM} = 17.74\) min.

1-(4-Chloro-phenyl)-ethyl acetate (2.6b):\(^{75}\)

\[
\text{\(1^H\)-NMR (300 MHz, CDCl}_3\) \(\delta \) 7.34-7.26 (m, 4H), 5.84 (q, \(J = 6.4\) Hz, 1H), 2.07 (s, 3H), 1.51 (d, \(J = 6.4\) Hz, 3H). \(13^C\)-NMR (50 MHz, CDCl}_3\) \(\delta \) 170.2 (s), 140.2 (s), 133.6 (s), 128.7 (d, 2C), 127.5 (d, 2C), 71.6 (d), 22.1 (q), 21.3 (q).
\]

Enantiomeric excess determination: \(\beta\)-DEX 120 column (30 m \(\times \) 0.25 mm \(\times \) 0.125 \(\mu\)m). Init. Temp.: 145 °C, \(T_{\text{det/inlet}} = 180 \degree\)C, \(t_S = 13.65\) min, \(t_R = 14.25\) min, \(t_{SM} = 20.24\) min.

1-(4-Nitro-phenyl)-ethyl acetate (2.6c):\(^{76}\)

\[
\text{\(1^H\)-NMR (300 MHz, CDCl}_3\) \(\delta \) 8.21 (d, \(J = 8.8\) Hz, 2H), 7.50 (d, \(J = 6.8\) Hz, 1H), 2.11 (s, 3H), 1.49 (d, \(J = 6.6\) Hz, 3H). \(13^C\)-NMR (50 MHz, CDCl}_3\) \(\delta \) 170.0 (s), 149.0 (s), 134.2 (s), 126.7 (d, 2C), 123.8 (d, 2C), 71.2 (d), 22.2 (q), 21.1 (q).
\]

Enantiomeric excess determination: \(\beta\)-DEX 120 column (30 m \(\times \) 0.25 mm \(\times \) 0.125 \(\mu\)m). Init. Temp.: 170 °C, \(T_{\text{det/inlet}} = 250 \degree\)C, \(t_S = 20.78\) min, \(t_R = 21.25\) min, \(t_{SM} = 26.27\) min.

1-Phenylethyl \(N,N\)-dimethyl carbamate (2.22):

\[
\text{\(1^H\)-NMR (300 MHz, CDCl}_3\) \(\delta \) 7.40-7.17 (m, 5H), 5.76 (q, \(J = 6.6\) Hz, 1H), 2.90 (s, 3H), 2.86 (s, 3H), 1.49 (d, \(J = 6.6\) Hz, 3H). \(13^C\)-NMR (50 MHz, CDCl}_3\) \(\delta \) 155.3 (s), 142.6 (s), 128.4 (d, 2C), 127.5 (d), 125.8 (d, 2C), 73.1 (d), 35.9 (q, 2C), 22.9 (q). MS, m/z (%): 193 (M\(^+\), 17%); HRMS for \(\text{C}_{11}\text{H}_{15}\text{NO}_{2}\), calcd: 193.110, found: 193.110. \(\alpha\)\(^{20}\)D = +5.0 (c 1.09, CHCl\(_3\), 94% ee).
\]

Enantiomeric excess determination: CP Chirasil-L-Val column (25 m \(\times \) 0.25 mm \(\times \) 0.25 \(\mu\)m). Init. Temp.: 100 °C, 10 min, 10 °C / min to 180 °C. \(T_{\text{det/inlet}} = 250 \degree\)C, split ratio 75:1, \(t_R = 9.76\) min, \(t_S = 10.12\) min, \(t_{SM} = 13.17\) min.
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1-Phenylethyl N,N-diethyl carbamate (2.33):

\[ ^1H\text{-NMR (300 MHz, CDCl}_3 \delta 7.37-7.13 (m, 5H), 5.82 (q, J= 6.6 Hz, 1H), 3.29 (q, J= 6.9 Hz, 4H), 1.53 (d, J= 6.6 Hz, 3H), 1.12 (t, J= 6.9 Hz, 6H).} \]

\[ ^{13}C\text{-NMR (50 MHz, CDCl}_3 \delta 155.2 (s), 142.7 (s), 128.4 (d, 2C), 127.4 (d), 125.8 (d, 2C), 72.7 (d), 41.4 (t, 2C), 22.9 (q), 13.9 (q, 2C). MS, m/z (%): 221 (M^+, 16.2%); HRMS for C_{13}H_{19}NO_2, calcd: 221.142, found: 221.142. [\alpha]^{20}D +4.6 (c 1.39, CHCl_3, 96% ee). \]

Enantiomeric excess determination: CP Chirasil-L-Val column (25 m × 0.25 mm × 0.25 μm). Init. Temp.: 100 °C, 20 min, 10 °C / min to 180 °C. T_{det/inlet} = 250 °C, split ratio 75:1, t_r = 20.42 min, t_s = 20.64 min, t_SM = 24.66 min.

1-Phenylethyl N,N-diisopropyl carbamate (2.34):

\[ ^1H\text{-NMR (300 MHz, CDCl}_3 \delta 7.34-7.16 (m, 5H), 5.80 (q, J= 6.6 Hz, 1H), 4.35-3.55 (br, 2H), 1.50 (d, J= 6.6 Hz, 3H), 1.32-1.03 (br, 12H).} \]

\[ ^{13}C\text{-NMR (50 MHz, CDCl}_3 \delta 155.0 (s), 142.8 (s), 128.3 (d, 2C), 127.4 (d), 126.0 (d, 2C), 72.6 (d), 45.7 (d, 2C), 22.8 (q), 20.8 (q, 4C). MS, m/z (%): 249 (M^+, 10.0%); HRMS for C_{15}H_{23}NO_2, calcd: 249.173, found: 249.174. \]

Enantiomeric excess determination: CP Chirasil-L-Val column (25 m × 0.25 mm × 0.25 μm). Init. Temp.: 100 °C, 20 min, 10 °C / min to 180 °C. T_{det/inlet} = 250 °C, split ratio 75:1, t_r = 23.44 min, t_s = 23.58 min, t_SM = 26.62 min.

1-(4-Nitro-phenyl)-ethyl N,N-diethyl carbamate (2.54):

\[ ^1H\text{-NMR (300 MHz, CDCl}_3 \delta 8.18 (d, J= 8.7 Hz, 2H), 7.48 (d, J= 8.7 Hz, 2H), 5.85 (q, J= 6.9 Hz, 1H), 3.30 (br, 4H), 1.53 (d, J= 6.9 Hz, 3H), 1.12 (br, 6H).} \]

\[ ^{13}C\text{-NMR (50 MHz, CDCl}_3 \delta 154.7 (s) 152.1 (s), 150.2 (s), 126.5 (d, 2C), 123.8 (d, 2C), 71.7 (d), 41.8 (t), 41.3 (t), 22.7 (q), 14.1 (q), 13.4 (q). MS, m/z (%): 266 (M^+, 21.5%); HRMS for C_{13}H_{18}N_2O_4, calcd: 266.127, found: 266.127. [\alpha]^{20}D -22.7 (c 0.90, CHCl_3, 98% ee). \]

Enantiomeric excess determination: CP Chirasil Dex CB column (25 m × 0.25 mm × 0.25 μm). Init. Temp.: 140 °C, 20 min, 10 °C / min to 180 °C. T_{det/inlet} = 250 °C, split ratio 25:1, t_r = 25.36 min, t_s = 25.48 min, t_SM = 28.07 min.

2-Hexyl N,N-diethyl carbamate (2.55):

\[ ^1H\text{-NMR (300 MHz, CDCl}_3 \delta 4.85-4.72 (m, 1H), 3.24 (br, J= 5.4 Hz, 4H), 1.55-1.22 (m, 6H), 1.18 (br, J= 6.0 Hz, 3H), 1.06 (t, J= 6.9 Hz, 6H), 0.87 (br, 3H).} \]

\[ ^{13}C\text{-NMR (50 MHz, CDCl}_3 \delta 155.8 (s), 71.3 (d), 41.2 (t, 2C), 36.0 (t), 27.6 (t), 22.5 (t), 20.3 (q), 14.0 (q), 13.8 (q, 2C). MS, m/z (%): 201 (M^+, 17.0%); HRMS for C_{11}H_{23}NO_2, calcd: 201.173, found: 201.172. [\alpha]^{20}D +13.1 (c 0.75, CHCl_3, 63% ee). \]

Enantiomeric excess determination: CP Chirasil Dex CB column (25 m × 0.25 mm × 0.25 μm). Init. Temp.: 100 °C, 20 min, 10 °C / min to 180 °C. T_{det/inlet} = 250 °C, split ratio 70:1, t_r = 20.13 min, t_s = 20.39 min, t_SM = 22.89 min.
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2-Phenylpropyl $N,N$-diethyl carbamate (2.56):

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 7.28-7.08 (m, 5H), 5.04-4.92 (m, 1H), 3.18 (br, 4H), 2.90 (dd, $J$ = 13.5, 6.6 Hz, 1H), 2.73 (dd, $J$ = 13.8, 6.6 Hz, 1H), 1.17 (dd, $J$ = 6.3, 1.5 Hz, 3H), 1.02 (br, 6H). $^{13}$C-NMR (50 MHz, CDCl$_3$) $\delta$ 155.4 (s), 137.9 (s), 129.5 (d, 2C), 128.2 (d, 2C), 126.2 (d), 71.8 (d), 42.6 (t), 41.1 (t, 2C), 19.7 (q), 13.6 (q, 2C). MS, $m/z$ (%): 233 (M$^+$, 3.9%); HRMS for C$_{14}$H$_{19}$NO$_2$: calcd: 233.142, found: 233.143. $\alpha$$_{D}^{20}$ +22.1 (c 2.10, CHCl$_3$, 73% ee).

Enantiomeric excess determination: CP Chirasil Dex CB column (25 m $\times$ 0.25 mm $\times$ 0.25 $\mu$m). Init. Temp.: 130 °C, 30 min, 10 °C / min to 170 °C. $T_{\text{det/inlet}}$ = 250 °C, split ratio 70:1, $t_{\text{minor}}$ = 32.70 min, $t_{\text{major}}$ = 32.85 min, $t_{\text{SM}}$ = 33.53 min.

1-Trimethylsilylethyl $N,N$-diethyl carbamate (2.57):

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 4.55 (q, $J$ = 7.8 Hz, 1H), 1.23 (d, $J$ = 7.5 Hz, 3H), 1.09 (t, $J$ = 6.9 Hz, 6H), 0.02 (s, 9H). $^{13}$C-NMR (50 MHz, CDCl$_3$) $\delta$ 156.5 (s), 64.5 (d), 41.5 (t, 2C), 16.1 (q), 13.8 (q, 2C), -4.0 (q, 3C). MS, $m/z$ (%): 217 (M$^+$, 1%); HRMS for C$_{10}$H$_{23}$NO$_2$Si: calcd: 217.150, found: 217.150. $\alpha$$_{D}^{20}$ +16.4 (c 1.54, CHCl$_3$, 43% ee).

Enantiomeric excess determination: CP Chirasil Dex CB column (25 m $\times$ 0.25 mm $\times$ 0.25 $\mu$m). Init. Temp.: 80 °C, 20 min, 10 °C / min to 170 °C. $T_{\text{det/inlet}}$ = 250 °C, split ratio 70:1, $t_{\text{minor}}$ = 25.08 min, $t_{\text{major}}$ = 25.22 min, $t_{\text{SM}}$ = 30.07 min.

**Procedure for the preparation of the racemic mixtures of 2.58 and 2.59:**

The ketone (1 mmol) was dissolved in MeOH 2.5 mL at 0 °C and NaBH$_4$ (38 mg, 1 mmol) was added in one portion while stirring. The stirring was continued for 15-20 min., until evolution of gas ceased, after which the solvent was removed under reduced pressure. The residue was taken in ether, washed with saturated solution of NH$_4$Cl, water, brine and dried over Na$_2$SO$_4$. After filtration through a plug of silica gel, the solvent was removed under reduced pressure affording the desired alcohol (91-90%, respectively).

The alcohol (0.8 mmol), dry pyridine (1 mL) and $N,N$-diethyl carbamoyl chloride (105 $\mu$L, 0.8 mmol) were stirred at 100 °C for 4 h. The reaction mixture was poured over a slurry of ice and extracted with ether (3 x 1 mL). The combined organic layers were washed with 10% aq. HCl solution, with a saturated aq. solution of NaHCO$_3$ and dried over MgSO$_4$. Removal of the solvent under reduced pressure followed by silica gel flash chromatography (pentane / ether 9:1) afforded the desired products (86-94%, 2.58 and 2.59, respectively).

**(E)-3-Nonen-2-yl $N,N$-diethyl carbamate (2.58):**

$^1$H-NMR (300 MHz, CDCl$_3$) $\delta$ 5.66 (dt, $J$ = 15.6, 6.9 Hz, 1H), 5.45 (dd, $J$ = 15.3, 6.6 Hz, 1H), 5.28-5.16 (m, 1H), 3.25 (br, 4H), 2.00 (q, $J$ = 6.9 Hz, 2H), 1.42-1.16 (m, 9H), 1.09 (t, $J$ = 6.9 Hz, 6H), 0.86 (t, $J$ = 6.6 Hz, 3H). $^{13}$C-NMR (50 MHz, CDCl$_3$) $\delta$ 155.4 (s), 151.0 (s), 132.2 (d), 130.3 (d), 71.4 (d), 41.4 (t, 2C), 32.1 (t), 31.3 (t), 28.7 (t), 22.5
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(t), 20.8 (q), 14.0 (q, 2C). MS, m/z (%): 241 (M⁺, 23.1%); HRMS for C_{14}H_{27}NO_{2}, calcd: 241.204, found: 241.205. [α]_{D}^{20} -4.7 (c 1.00, CHCl₃, 97% ee).

Enantiomeric excess determination: Chiraldex α-TA column (30 m × 0.25 mm × 0.125 μm). Init. Temp.: 95 °C, 150 min, 10 °C / min to 180 °C. T_{det/inlet} = 200 °C, tᵦ = 134.1 min, tᵣ = 136.1 min, t_{SM} = 149.6 min. Saturated racemic product: t = 130.4, 132.0 min.

(\textit{E})-4-Phenyl-3-buten-2-yl \textit{N,N}-diethyl carbamate (2.59): \textit{^1}H-NMR (300 MHz, CDCl₃) δ 7.40-7.11 (m, 5H), 6.54 (d, J= 15.9, 1H), 6.18 (dd, J= 15.9, 6.3 Hz, 1H), 5.47-5.35 (m, 1H), 3.25 (brq, J= 6.6 Hz, 4H), 1.37 (d, J= 6.6 Hz, 3H), 1.08 (t, J= 6.9 Hz, 6H). \textit{^13}C-NMR (50 MHz, CDCl₃) δ 155.3 (s), 136.6 (s), 130.5 (d), 128.5 (d, 2C), 127.6 (d), 126.5 (d, 2C), 71.2 (d), 41.3 (t, 2C), 20.7 (q), 14.0 (q, 2C). MS, m/z (%): 247 (M⁺, 26.5%); HRMS for C_{15}H_{21}NO_{2}, calcd: 247.157, found: 247.158.

Enantiomeric excess determination: Chiraldex α-TA column (30 m × 0.25 mm × 0.125 μm). Init. Temp.: 150 °C, 50 min, 1 °C / min to 180 °C. T_{det/inlet} = 200 °C, tᵦ = 43.8 min, tᵣ = 44.8 min, t_{SM} = 70.8 min. Saturated racemic product: t = 27.5, 27.8 min.

General procedure for carbamate deprotection:\textsuperscript{70}

1-Phenylethanol (2.74): To a solution of 1-phenylethyl \textit{N,N}-dimethyl carbamate (2.6a) (41.1 mg, 0.21 mmol) in ether (3 mL) at 0 °C, LiAlH₄ (12 mg, 0.32 mmol, 1.5 eq.) was added in one portion and the mixture was allowed to reach room temperature. After stirring for two hours the reaction was quenched with Na₂SO₄·10H₂O. After filtration of the solids over celite, the solvent was removed under reduced pressure. The crude mixture was purified by silica gel flash chromatography (heptane / ethyl acetate 3:1) affording the desired compound (81%). Analytical data were in agreement with a commercial sample. \textit{^1}H-NMR (300 MHz, CDCl₃) δ 7.34-7.20 (m, 5H), 4.80 (q, J= 6.6 Hz, 1H), 2.55 (s br, 1H), 1.43 (d, J= 6.6 Hz, 3H). Absolute configuration determination: β-DEX 120 column (30 m × 0.25 mm × 0.125 μm). Init. Temp.: 105 °C, T_{det/inlet} = 150 °C, tᵦ = 27.26 min, tᵣ = 29.64 min.

4-Phenyl-butan-2-ol (2.75):\textsuperscript{80} (E)-1-Methyl-3-phenyl-allyl \textit{N,N}-diethyl carbamate (2.59) (50 mg, 0.20 mmol) was reacted as described in the general procedure using THF as solvent. As the reaction appeared not to proceed, another equivalent of LiAlH₄ was added and the reaction mixture was allowed to stir at room temperature overnight and at 60 °C for two hours. After the described work-up, the crude mixture was purified by silica gel flash chromatography (pentane / ether 7:3) affording 4-phenyl-butan-2-ol (56%).
and not the expected (E)-4-phenyl-but-3-en-2-ol. Data were in agreement also with the product obtained from the reduction of the corresponding ketone with NaBH₄.

1H-NMR (300 MHz, CDCl₃) δ 7.29-7.09 (m, 5H), 3.85-3.72 (m, 1H), 2.80-2.56 (m, 2H), 1.81-1.67 (m, 2H), 1.34 (br s, 1H), 1.19 (dd, J= 6.2, 1.8 Hz, 3H).

The absolute configuration was determined by HPLC: Chiralpack AD column, heptane/i-PrOH 95:5. tᵣ = 8.45 min, tₛ = 11.31 min.

2.13 References


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(14) Peña, D.; unpublished results. This ligand was successfully used in the Rh-catalyzed asymmetric hydrogenation of β-dehydroamino esters (Ref. 12c).


(39) Persistent contamination by carbamoyl chloride has been also reported elsewhere. Olofson, R. A.; Cuomo, J. *Tetrahedron Lett.* 1980, 21, 819.
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(40) The product is suspected to be volatile as a conversion of 82% was determined by NMR and no side products were visible.


(43) An example of alkylation of an enol carbamate in α-position mediated by HMPA was also found in the literature: Kocienski, P.; Dixon, N. J. Synlett. 1989, 52.


(46) Reverse order of addition, between NaOH and I2, was reported to yield exclusively cis-1-alkenyl iodides. Steward, S. K.; Whiting, A. Tetrahedron Lett. 1995, 36, 3929.


(49) de Vries, J. G. Chem. Eur. J. 2006, accepted for publication. For more references on this subject, see also Chapters 1 and 3.


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(59) Prepared according to the procedure described in Ref. 12a. A mistake was found for the $^1$H-NMR in the Ref. 58c.


(62) Prepared according to the procedure given in Ref. 15.

(63) Prepared according to a literature procedure for the synthesis of vinyl carbonates: Ref. 26.

(64) Spectral data in agreement with the literature: Peters, J. G.; Seppi, M.; Fröhlich, R.; Wibbeling B.; Hoppe D. Synthesis 2002, 3, 381.

(65) Adapted to preparative scale from literature procedures: Ref. 35, 37, 38


(67) Adapted synthesis from a literature procedure: Ref. 31


(69) Original procedure described and data in agreement with the literature: Ref. 31.


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