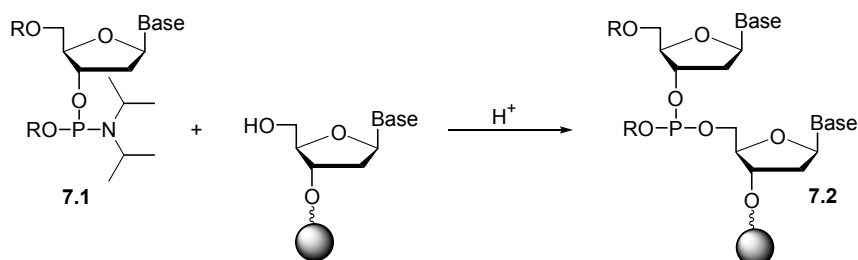


## Chapter 7

# Parallel synthesis of phosphoramidite ligand libraries for high throughput experimentation

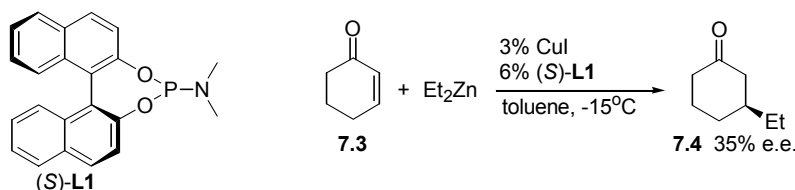
### 7.1 Introduction

Among the first and best known applications of phosphoramidites (a trivalent phosphorus compound with  $(\text{RO})_2\text{PNR}_2$  as a general structure) is their role as activated monomers (7.1) for the solid phase oligonucleotide synthesis (7.2) (Scheme 7.1).<sup>1</sup>



**Scheme 7.1** Phosphoramidite as an activated monomer in oligonucleotide synthesis.

In 1994 phosphoramidite **L1** (MonoPhos) was developed by Ron Hulst in our group as a chiral derivatizing agent for the e.e. determination of alcohols and amines by means of  $^{31}\text{P}$ -NMR,<sup>2</sup> but it proved to be unreactive towards nucleophilic attack. This unexpected high stability in combination with initial reports about the use of trivalent phosphorus compounds in asymmetric catalysis,<sup>3,4</sup> led in 1996 to the first application of **L1** by André de Vries in our group as a chiral ligand for the copper-catalyzed asymmetric conjugate addition (ACA) of diethylzinc to cyclohexenone (7.3) (Scheme 7.2).<sup>5</sup>



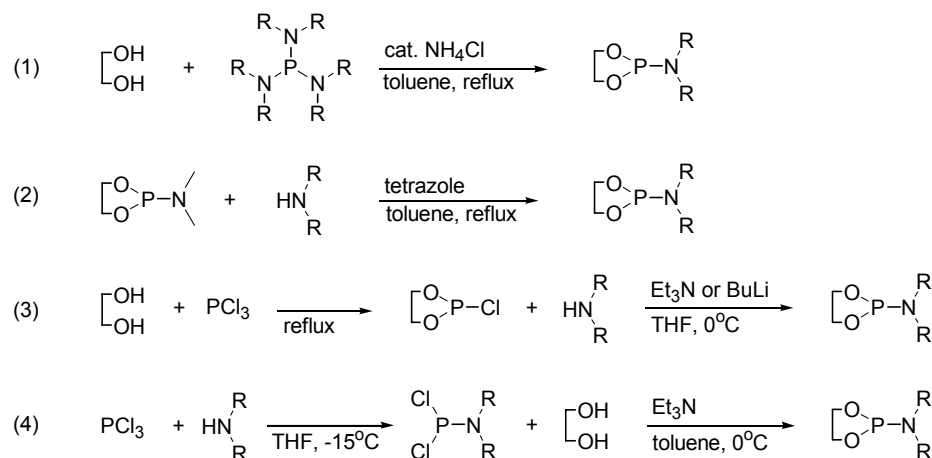
**Scheme 7.2** Phosphoramidite as a chiral ligand in the conjugate addition.

Part of this Chapter has been published: A. Duursma, L. Lefort, J. A. F. Boogers, A. H. M. de Vries, J. G. de Vries, A. J. Minnaard, B. L. Feringa *Org. Biomol. Chem.*, **2004**, 2, 1682-1684.

This encouraging result eventually led to the development of chiral monodentate phosphoramidites as a highly successful novel class of ligands for various catalytic reactions as outlined in Chapter 1.

## 7.2 Synthetic routes to phosphoramidites

The widespread use of chiral monodentate phosphoramidites as ligands for asymmetric catalysis is stimulated by their facile and modular synthesis. There are currently four general routes for the preparation of these ligands (Scheme 7.3).<sup>6</sup>

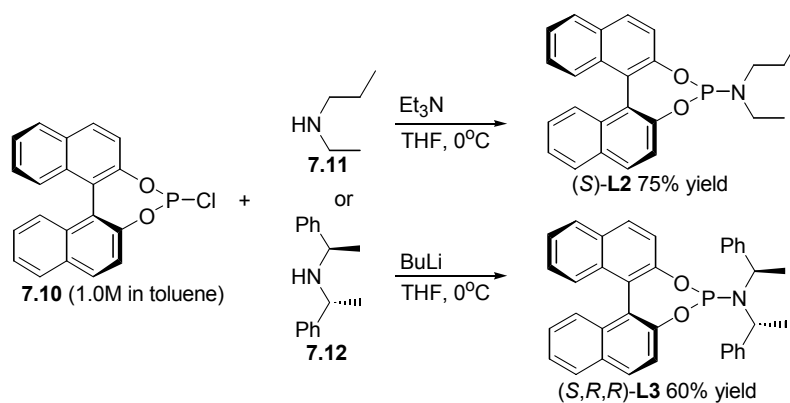


**Scheme 7.3** Preparation of monodentate phosphoramidite ligands.

The most efficient route is the phosphorylation of chiral diols with a phosphorous triamide.<sup>2</sup> Under the influence of a catalytic amount of ammonium chloride, the phosphoramidites are obtained in a single step and excellent yields (Equation 1 in Scheme 7.3). Although this procedure is limited to commercially available phosphorous triamides as a source of the amine moiety, the dimethylamino-based phosphoramidites can serve as a starting point for the synthesis of phosphoramidites with other substituents at the amine moiety. Inspired by the alcoholysis of phosphoramidites in the solid phase oligonucleotide synthesis (Scheme 7.1), a procedure was developed by Adri Minnaard in our group, which is based on amine exchange using tetrazole as a catalyst.<sup>7</sup> This transamination process can be used for the synthesis of phosphoramidites based on non-bulky and non-volatile amines (Equation 2).<sup>8</sup> By far the most versatile route is a two step procedure starting with the synthesis of a phosphorochloridite by the reaction of a diol with phosphorus trichloride (PCl<sub>3</sub>). If the phosphorochloridite is subsequently allowed to react with a primary or secondary amine in the presence of Et<sub>3</sub>N, the corresponding phosphoramidite is obtained in good yield and under mild conditions. For the case of sterically demanding amines the use of its lithiated equivalent is required (Equation 3).<sup>5,9</sup> This procedure can also be reversed by starting with



Using  $\text{PCl}_3$  as the solvent, BINOL (**7.5**) is refluxed overnight after which the excess  $\text{PCl}_3$  is removed by azeotropic distillation to give phosphorochloridite **7.10** quantitatively as a white solid on gram scale. There is no need for a base since the hydrochloric acid produced is removed by the high temperature ( $78^\circ\text{C}$ ), which avoids a purification step for the removal of salts. This procedure could also be employed for the synthesis of the phosphorochloridites based on diols **7.6-7.8**. The phosphorochloridites of catechol (**7.9**), glycol and pinacol are commercially available. Another main advantage of this method is that the obtained phosphorochloridites can be stored as a stock solutions in anhydrous toluene, which are stable for at least 6 months. These stock solutions can be used in the divergent synthesis of various phosphoramidites, making it possible to obtain 300 mg of two different analytically pure phosphoramidites, such as **L2** and **L3**, in one day (Scheme 7.6).



**Scheme 7.6** Phosphoramidite synthesis using a stock solution.

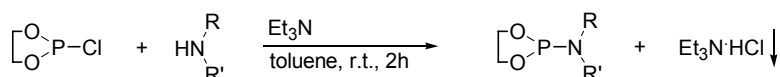
For simple primary and secondary amines, like **7.11**, triethylamine is preferred as a base. A high purity of the amine is essential in order to obtain a high yield, and therefore they are distilled immediately before use. For more sterically demanding amines like **7.12**, butyllithium is the most suitable base, although it can lead to the formation of more side products and consequently a slightly lower yield.

#### 7.4 Synthesis of solution phase phosphoramidite ligand libraries

The above mentioned procedure leads to a highly practical synthesis for large quantities (gram scale) of individual phosphoramidite ligands. During the optimization of phosphoramidite based catalysts, as described in the preceding chapters, there is, however, a need for a large number of structurally diverse phosphoramidites and relatively small quantities are sufficient. Combinatorial techniques such as the one-pot multi-substrate screening (Chapter 2) and the monodentate ligand combination approach (Chapter 5) speed up the catalyst optimization process.<sup>15,16</sup> If the phosphoramidite ligands could in addition also be synthesized in a combinatorial fashion it would dramatically decrease the time

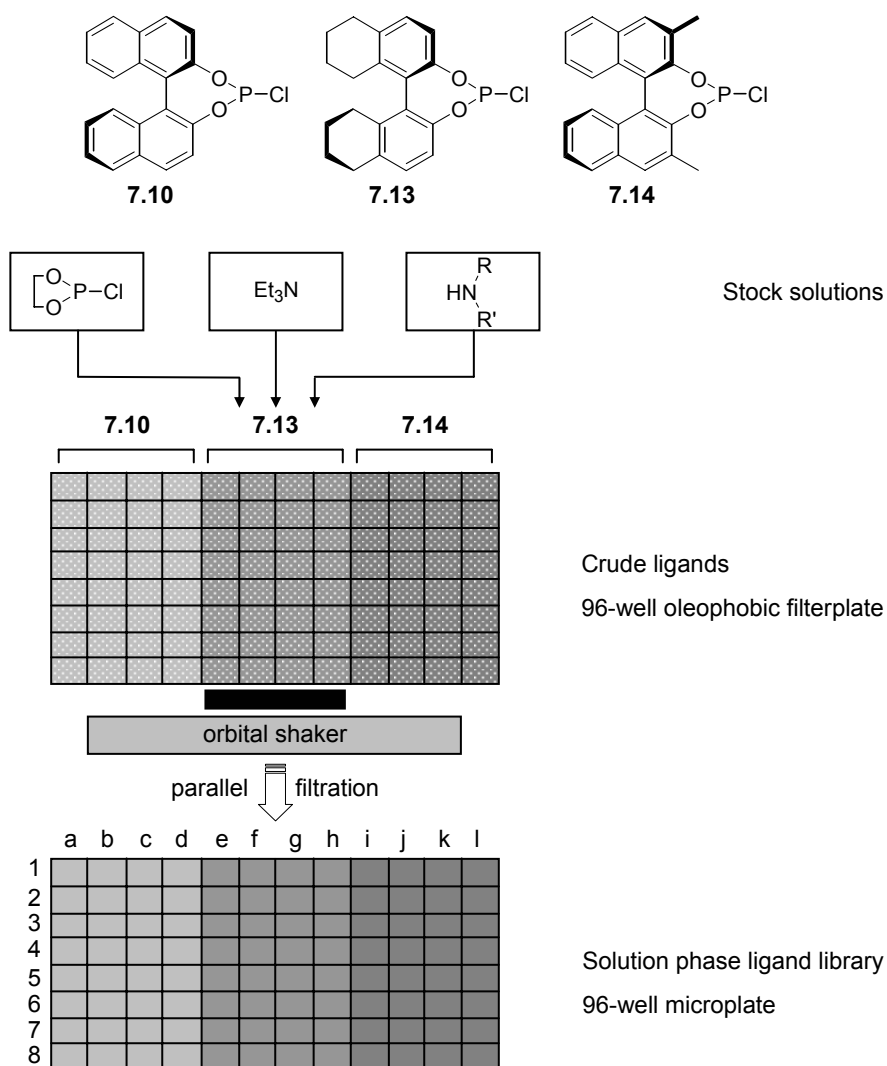
period needed for catalyst optimization. This has recently been demonstrated by the group of de Vries, which screened a library of 32 different phosphoramidite ligands in the rhodium catalyzed asymmetric hydrogenation.<sup>17</sup> We have used their procedure for the synthesis of a solution phase ligand library of 96 different phosphoramidites.<sup>18</sup>

As outlined in Chapter 1.7, the most effective approach in combinatorial asymmetric catalysis is to perform parallel reactions (one catalyst per vial) followed by high throughput screening.<sup>19-21</sup> The ligands in the libraries screened by this approach have mostly been synthesized one at a time or by automated solid phase procedures.<sup>22</sup> Whereas the former method can be very time consuming, in case of the latter the translation of solution phase chemistry to the solid phase and vice versa can be quite problematic,<sup>23</sup> as illustrated by recent examples of solid phase bound phosphoramidites.<sup>24-26</sup> We used an automated solution phase parallel synthesis for the preparation of a 96 member phosphoramidite ligand library, since it allowed the use of existing solution phase synthetic methodology for the preparation of phosphoramidites. The synthesis of the phosphoramidites could be further simplified and made suitable for automation by performing the reaction at room temperature (Scheme 7.7).



**Scheme 7.7** Phosphoramidite ligand synthesis at room temperature.

According to Scheme 7.7, the reaction of stoichiometric amounts of phosphorochloridite, amine and base lead to the formation of the desired ligand and a precipitate of the triethylamine HCl salt. A simple filtration gives a toluene solution of the phosphoramidite ligand. The automation of the synthesis is achieved by using all reagents as stock solutions, which are transferred by a liquid handling robot placed in a glove box. The chromatography normally performed at the end of the synthesis is replaced by filtration, not only because it enables the use of an automated procedure, but also because phosphoramidites based on primary and/or aromatic amines tend to decompose during this step. For the parallel synthesis of the 96 ligand library according to Figure 7.1, toluene stock solutions of three phosphorochloridites based on BINOL (**7.10**), 8H-BINOL (**7.13**) and 3,3'-dimethyl-BINOL (**7.14**) were added to a 96-well oleophobic filterplate in three areas of 32 wells, respectively (Figure 7.1).











































**Figure 7.1** Phosphoramidite ligand library synthesis.

The subsequent addition of a stoichiometric amount of triethylamine to each of the 96 wells was followed by the addition of a stoichiometric amount of 32 different amines (Table 7.1) to each area of phosphorochloridite, leading to 96 different crude phosphoramidite ligands based on three diols and 32 amines. After two hours of agitation at room temperature on an

orbital shaker, the precipitated triethylamine hydrochloric acid salts were removed via parallel filtration. By placing the oleophobic filterplate on top of a 96-well microplate and applying a vacuum, a ligand library of 96 clear stock solutions of phosphoramidites in toluene was obtained.

Table 7.1 Amines used

	a	e	i	b	f	j	c	g	k	d	h	l
1												
2												
3												
4												
5												
6												
7												
8												

In order to create a ligand library that could be used for lead finding, a large variety of amines was used. This gave three types (**1a-8d**, **1e-8h**, and **1i-8l**) of structurally diverse phosphoramidites based on primary and secondary amines with chiral and achiral substituents as well as aromatic and aliphatic substituents. <sup>31</sup>P-NMR of phosphoramidite ligands **3c** and **3k** demonstrated that they were formed with >90% purity.

## 7.5 Applications of solution phase phosphoramidite ligand libraries

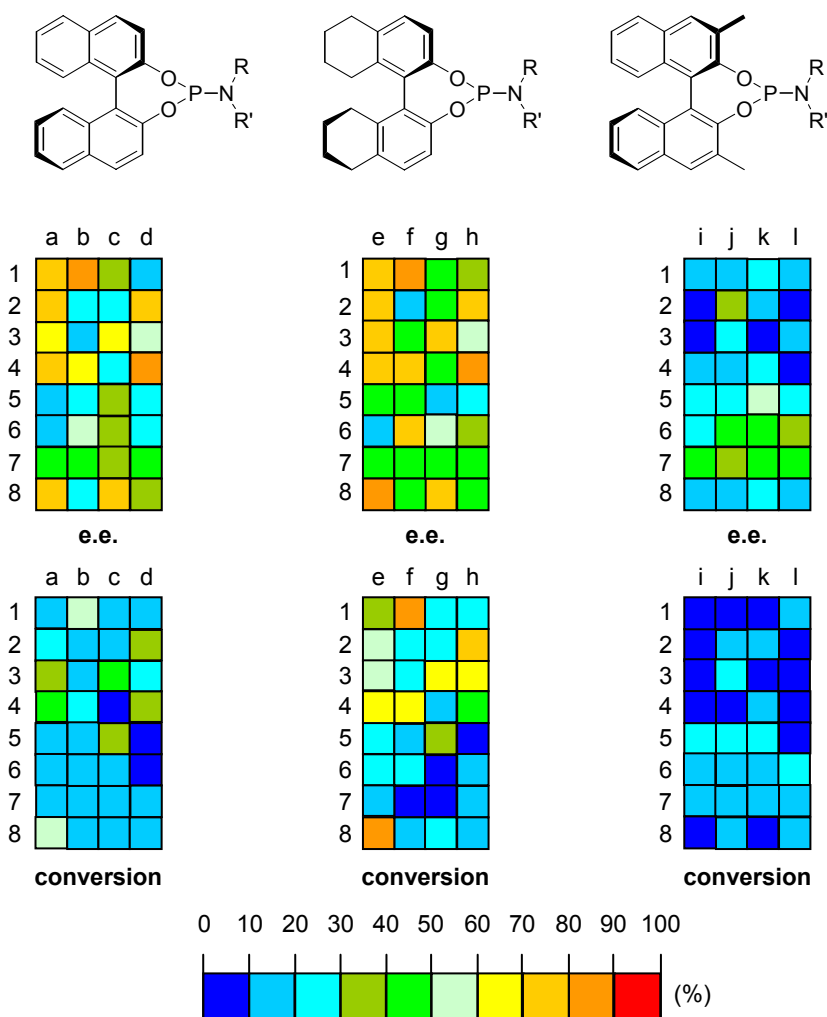
Since the ligand library was designed for lead finding, the rhodium catalyzed asymmetric conjugate addition (ACA) of potassium vinyltrifluoroborate (**7.15**) to cyclohexenone (**7.3**) provided an ideal case for the screening of the library (Table 7.2). Optimization of the phosphoramidite ligand structure for this reaction via rational design as described in Chapter 6, led to ligand **1f**, based on 8H-BINOL and diethylamine, as the most successful phosphoramidite. Phosphoramidites based on primary and aromatic amines, however, were not examined during this optimization, in part due to their more troublesome purification. In order to establish a valid protocol for the screening of the entire library, four ligands out of the library were used in the ACA of **7.15** to **7.3** and the results were compared with those obtained previously with phosphoramidites that were synthesized on a preparative scale and purified by column chromatography (Table 7.2).

**Table 7.2** Comparison of phosphoramidite ligands.

ligand (position)	purified ligands		solution phase ligands	
	conversion (%) <sup>a</sup>	e.e. (%) <sup>a</sup>	conversion (%) <sup>a</sup>	e.e. (%) <sup>a</sup>
<b>1f</b>	99	88	55	86
<b>8e</b>	96	86	72	83
<b>4d</b>	66	85	25	77
<b>3c</b>	86	66	35	64

<sup>a</sup>Determined by chiral GC.

This demonstrated that the results obtained with the unpurified solution phase phosphoramidite ligands are close to those obtained with purified ligands. More importantly, the trend in e.e. values remains intact, allowing comparison of the ligands with the library. The lower conversion can be attributed to the fourfold lower concentration of the reagents in case of the solution phase ligands, but this is not a critical issue since the e.e. values are independent of the conversion. To our delight the presence of 5 vol.% toluene, from the ligand stock solution, does not have a negative effect upon the e.e. After these encouraging results, the entire solution phase ligand library was tested in the reaction of Table 7.2 with an automated procedure. Using the liquid handling robot, a part of the stock solution in each well of the entire library was transferred to 96 corresponding reaction vials, followed by an ethanol stock solution of the rhodium precursor and substrate **7.3**. After the addition of trifluoroborate **7.15**, the vials were sealed, placed in a Premex 96-Multi Reactor,<sup>27</sup> and heated at reflux for two hours. Analysis of the reaction mixture by chiral GC gave the results shown in figure 7.2.

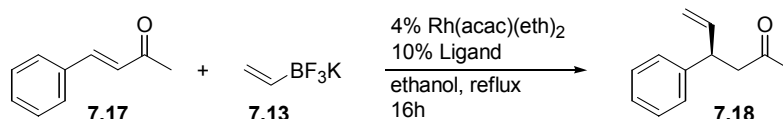


**Figure 7.2** Results of the library screening for 7.3.

Due to the large number of results, 96 e.e. values and 96 conversions, no quantitative data are given here (see Experimental section) but a specific color was assigned to each interval of 10% of e.e. and conversion. This allows a quick visual identification of the most active and selective catalysts (orange/red). All the phosphoramidites based on 3,3'-dimethyl-BINOL (7.7) show a low activity and selectivity for the ACA of 7.15 to 7.3, with ligand **5k** based on aniline as the best with 21% conversion and 50% e.e. This is in line with the low

activity and selectivity observed for 3,3'-disubstituted phosphoramidite ligands in the rhodium-catalyzed ACA of phenylboronic acid to nitrostyrenes (Chapter 4). The BINOL (**7.5**) and 8H-BINOL (**7.6**) based ligands perform much better in most cases. They display almost identical structure-selectivity and structure-activity relationships. Catalysts based on the latter ligands lead to a slightly higher e.e. and about 30% more conversion than the former. The use of ligands based on primary aromatic amines results in low conversions (up to 39% for **5g**) and e.e. values (up to 35% for **1h**). Phosphoramidites based on primary aliphatic amines lead to higher e.e. values (up to 53% for **6g**), but lower conversions (up to 19% for **6k**). Secondary aromatic amines lead to moderate e.e. values and low conversions (48% e.e., 22% conversion for **5e**). The best results are obtained with phosphoramidite ligands based on secondary aliphatic amines, and both high conversions and e.e. values are obtained. Phosphoramidite **1f** proved to be the most effective ligand, giving 87% e.e. and 81% conversion. Amines used for the synthesis of ligands **3b,f,j**, **3d,h,l**, and **4a,e,i** were used as mixtures of stereoisomers, leading to diastereomeric ligands and catalysts. The fact that **4a** and **4e** are still able to achieve high conversions (up to 62%) and e.e. values (up to 73%), suggests that the screening of the individual stereoisomers could lead to more effective catalysts. This point is illustrated by the fact that the use of phosphoramidites **2d** and **2h** lead to higher conversions and e.e. values than **3a** and **3i**.

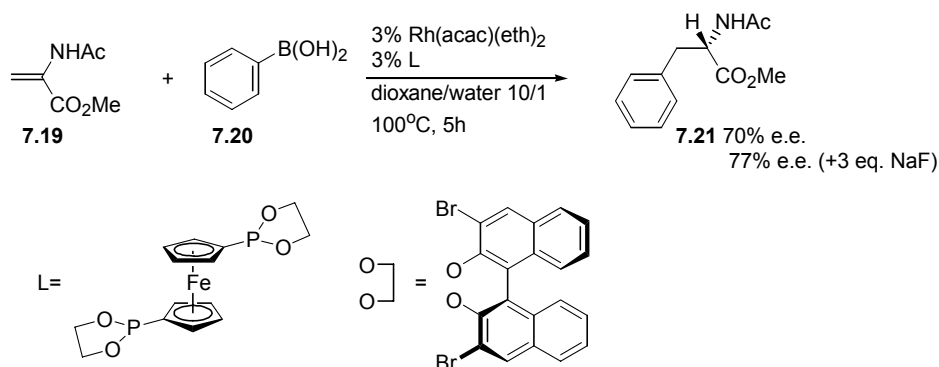
In addition to cyclic enone **7.3**, the more challenging acyclic enone benzylidene acetone (**7.17**) was used in the screening of the library. This represents a substrate which, to the best of our knowledge, has never been used before in the ACA of alkenyl groups (Scheme 7.8).



**Scheme 7.8** Rhodium-catalyzed ACA of **7.13** to **7.17**.

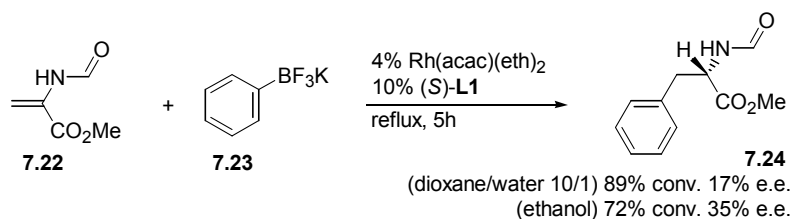
The reaction was performed overnight in a similar fashion as for **7.3**, and the conversions and e.e. values were determined by chiral GC. The results are shown in Figure 7.3 (p. 146), with colors assigned to each interval of 5% due to the lower e.e. values. As in the case of cyclic enone **7.3**, phosphoramidites based on 3,3'-dimethyl-BINOL (**7.7**) lead to low conversions and e.e. values (up to 22% and 29% for **4l**), even after 16 hours. Ligands based on BINOL (**7.5**) and 8H-BINOL (**7.6**) lead to much more effective catalysts that are able to reach full conversion. But in contrast to the previous case, the former lead to slightly higher e.e. values. The most effective ligands, which result in moderate e.e. values so far, are based on cyclic amines containing ester substituents such as **3d** (42% e.e.) and **4b** (44% e.e.). The screening of a more focused library based on this type of amine, including the single stereoisomers, will undoubtedly lead to the identification of a more selective catalyst for this reaction.

In a seminal paper from the group of Reetz in 2001,<sup>28</sup> it was demonstrated that, under the influence of a rhodium-diphosphonite catalyst, the protonation step in the catalytic cycle of the conjugate addition could be used for the introduction of enantioselectivity (see Chapter 4.2 for the mechanism). The conjugate addition of phenylboronic acid (**7.20**) to **7.19**, under standard conditions for this type of reaction, gave **7.21** with 70% e.e. (Scheme 7.9).



**Scheme 7.9** Conjugate addition with subsequent enantioselective protonation.

When 3 equivalents of sodium fluoride are added, the e.e. increases to 77%, which suggests that the in situ formation of a phenyltrifluoroborate is responsible for this effect. This conjugate addition of arylboron compounds followed by enantioselective protonation holds promise as the most direct route to phenylalanine derivatives, especially when the substrate contains the easily removable formyl protecting group as in **7.22**. To see whether a rhodium-phosphoramidite catalyst is suitable for this purpose, the conjugate addition of potassium phenyltrifluoroborate (**7.23**) in two different solvents was investigated (Scheme 7.10).



**Scheme 7.10** Rh-phosphoramidite catalyzed conjugate addition and enantioselective protonation.

To our delight, a catalyst based on Rh(acac)(eth)<sub>2</sub> and phosphoramidite **L1** gave high conversions to **7.24**, and a moderate e.e. of 35% when ethanol was used as solvent and proton donor. Screening of the ligand library under these conditions gave the results shown in Figure 7.4 (p. 147).

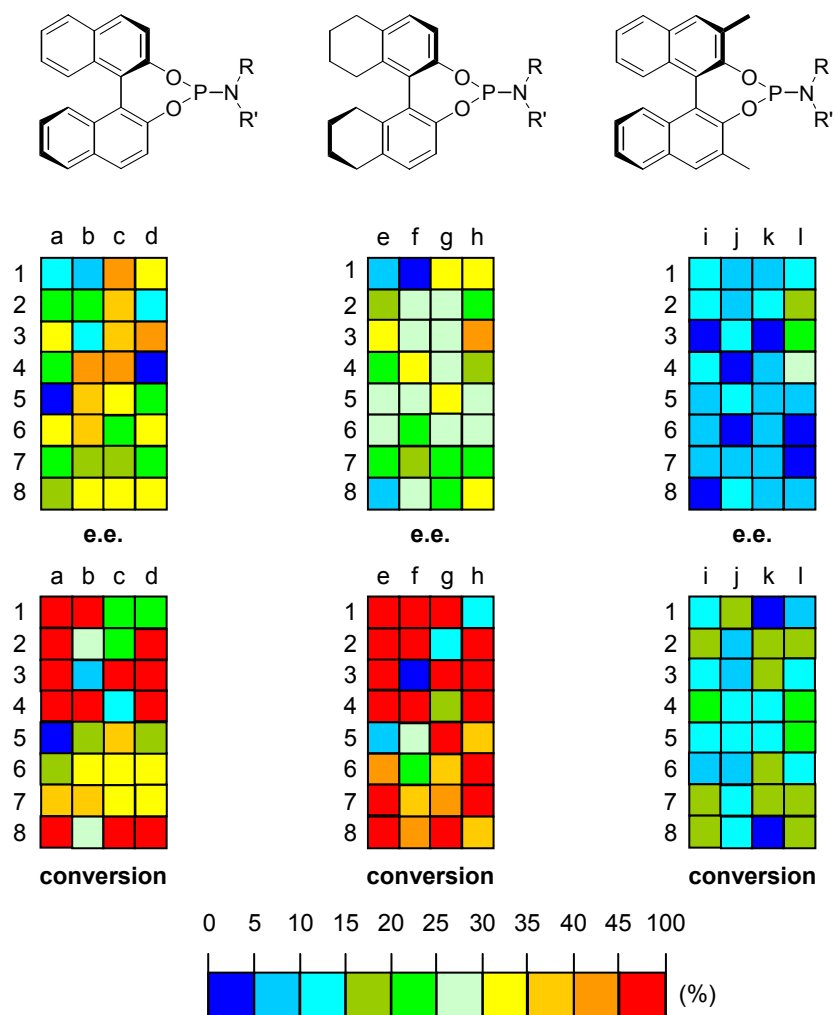
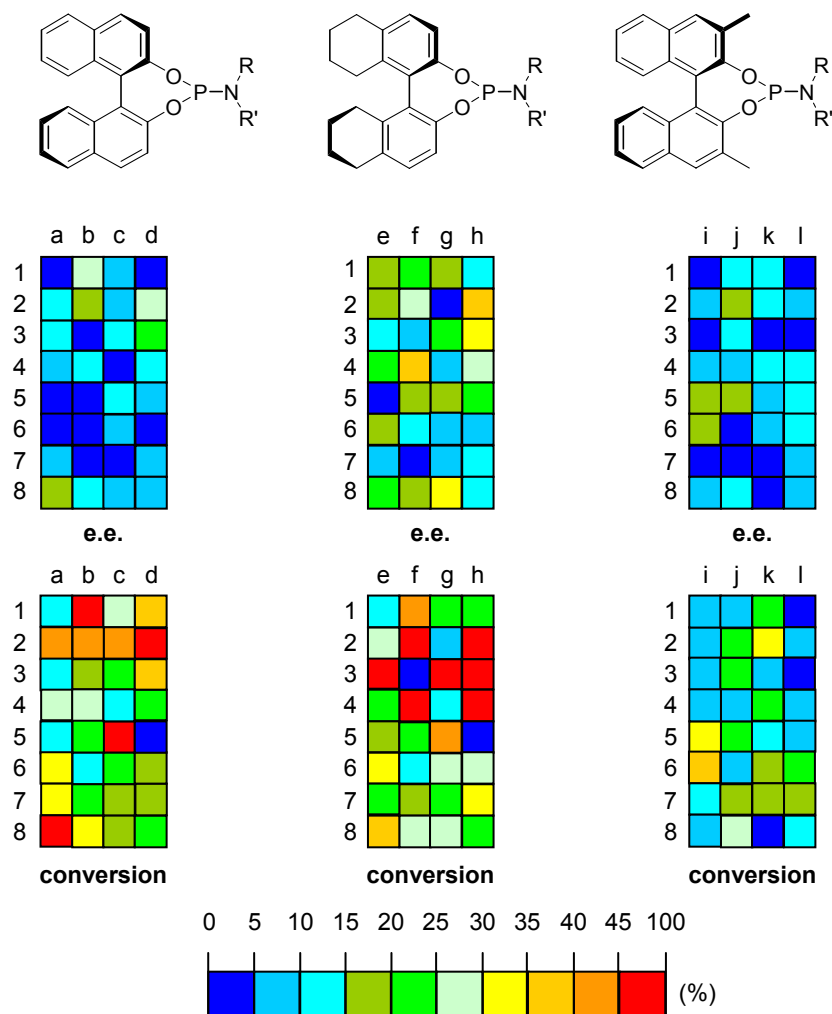


Figure 7.3 Results of the library screening for 7.17.

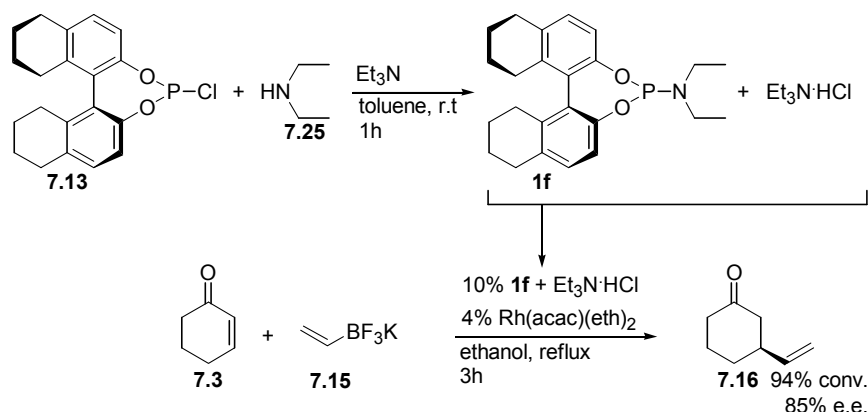


**Figure 7.4** Results of the library screening for 7.22.

The e.e. values obtained with phosphoramidite ligands based on 8H-BINOL (7.6) as the backbone, are clearly superior to those based on BINOL (7.5) and 3,3'-dimethyl-BINOL (7.7), although the improvement with respect to the results using **L1** is small. These results suggest that the general structure of an effective ligand for this reaction has to be based on 8H-BINOL and a functionalized cyclic amine, such as **2h** (38% e.e.), **3h** (32% e.e.), and **4f** (35% e.e.).

## 7.6 Cascade synthesis and catalysis

In the automated synthesis of solution phase phosphoramidite libraries, the purification of the ligands is restricted to a simple filtration in order to remove the precipitated triethylamine HCl salt (Figure 7.1). The removal of this salt proved to be essential, because omitting the filtration led to inactive catalysts in the rhodium-catalyzed asymmetric hydrogenation.<sup>17</sup> The filtration and subsequent transfer of the ligand stock solutions to the reaction vials are in fact two additional steps that are performed *after* the actual ligand has been synthesized. If the filtration step could be avoided, it would lead to an even simpler protocol. The detrimental effect of the triethylamine HCl salt in the rhodium-catalyzed hydrogenations can be attributed to the acidic properties which might affect the ligand, or the interaction of chloride with rhodium. On the basis of the results described in Chapter 6.5, these effects are not expected to inhibit the ACA of organotrifluoroborates. Therefore we decided to perform a cascade experiment in which the synthesis of the ligand is followed by the in-situ catalyst formation and a subsequent reaction in one pot (Scheme 7.11).

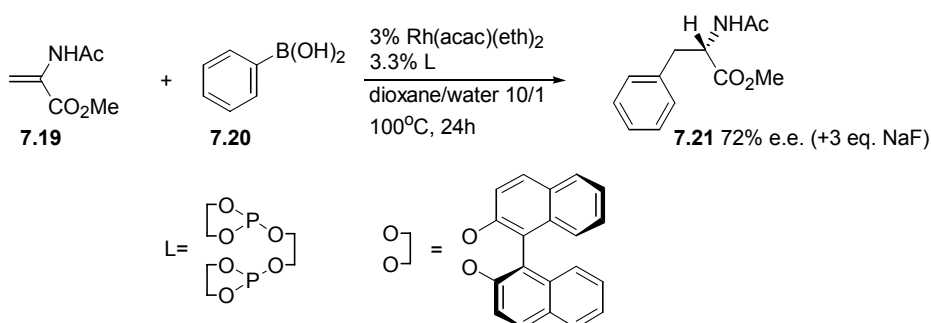


**Scheme 7.11** Cascade synthesis and catalysis for the ACA of **7.15**.

The ligand was synthesized by stirring equimolar amounts of toluene stock solutions of phosphorochloridite **7.13**, triethylamine, and diethylamine (**7.25**) at room temperature. After 1 hour, ethanol stock solutions of the rhodium precursor and reagents were added to the same tube, and heated at reflux for 3 hours. Chiral GC analysis showed almost complete conversion and a high e.e. of 85% for **7.16**, which is nearly identical to the results obtained with the purified and the solution phase ligand **1f** (81% conv., 87% e.e.). The apparently negligible effect of the triethylamine HCl salt upon the ACA of organotrifluoroborates allows an even faster evaluation of a rhodium-phosphoramidite catalyst for this type of reaction. This procedure might also be applied in the copper-catalyzed ACA of dialkylzinc reagents, because traces of chloride can even have a beneficial effect upon this type of reaction (Chapter 2.5). It might even be extended to the rhodium-catalyzed asymmetric hydrogenations when an efficient scavenger of the triethylamine HCl salt is added to the reaction mixture.

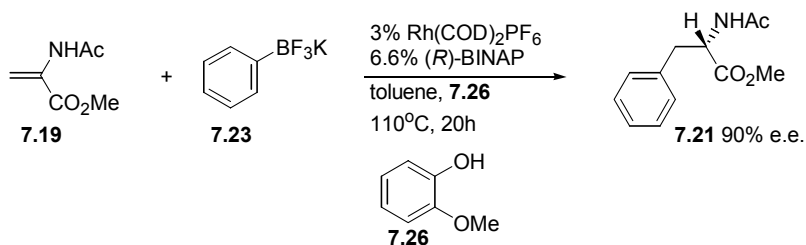
## 7.7 Further developments

During the course of our research the group of Frost demonstrated that the diphosphite, which was formed as a side product in our initial phosphoramidite synthesis (Scheme 7.4), is actually a good ligand for the tandem conjugate addition – enantioselective protonation (Scheme 7.12).<sup>29,30</sup>



**Scheme 7.12** Diphosphite as a chiral ligand.

Using the same procedure as employed by the group of Reetz, almost identical results are obtained for **7.21** with the diphosphite ligand. Shortly thereafter the group of Darses and Genet employed potassium aryltrifluoroborates in this reaction, and obtained e.e. values of up to 90% using BINAP as a chiral ligand (Scheme 7.13).<sup>31,32</sup>



**Scheme 7.13** Guaiacol as a proton source.

In order to obtain a high e.e. the use of 1 equivalent of guaiacol (**7.26**) as the proton source was essential, because the use of other proton sources such as water gave much lower e.e. values.

## 7.8 Conclusions

Of the four synthetic routes for obtainment of phosphoramidite ligands, the phosphorylation of chiral diols with a phosphorus triamide is a highly efficient route, but limited by the small number of commercially available phosphorus triamides. Phosphoramidites with other substituents at the amine moiety can be easily synthesized on gram scale via a

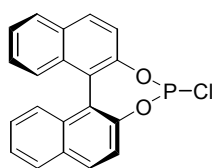
divergent synthesis starting with a phosphorochloridite. These phosphorochloridites are commercially available or quickly obtained by refluxing a diol in  $\text{PCl}_3$  as a solvent. For the screening and optimization of phosphoramidite based catalysts, solution phase libraries of phosphoramidite ligands are a powerful tool. A library of 96 different phosphoramidites was synthesized via an automated parallel procedure, and screened in enantioselective C-C and C-H bond formation. Although the ligands within the library have been synthesized on a relatively small scale (~20 mg each), it is sufficient for the screening of 4 to 5 different reactions. In case of the ACA of potassium vinyltrifluoroborate to cyclohexenone, the results of the solution phase library confirmed within 3 days those obtained by rational design in 3 months. For the ACA of potassium vinyltrifluoroborate to benzylidene acetone promising results have been found for ligands based on cyclic amines with ester substituents, suggesting that a second (weakly) coordinating group might be favorable. The screening of a more focused library might lead to a highly selective catalyst for the ACA of organoboron compounds to acyclic enones. Application of the library in the rhodium-phosphoramidite catalyzed tandem conjugate addition – enantioselective protonation revealed that ligands based on functionalized cyclic amines were also the most effective for this reaction. In this case the screening of a more focused library in combination with several proton donors is likely to improve the moderate e.e. values obtained so far. The most time consuming step in these experiments is the determination of the e.e. values and the conversions. With the use of short chiral GC runs (< 15 min) in combination with an autosampler, it was possible to perform these analyses in about 24 h. For the case of less volatile compounds an analogous chiral HPLC method would need to be applied. The use of a genuine high throughput analysis (> 1000 samples a day),<sup>21,33</sup> preferably based on a color assay,<sup>34</sup> would be highly effective. Although the removal of the triethylamine HCl salt is essential for the screening of ligand libraries in rhodium-phosphoramidite catalyzed hydrogenations, it can be omitted for the rhodium-phosphoramidite catalyzed ACA of potassium organotrifluoroborates. This led to an experiment in which the phosphoramidite ligand is synthesized, complexed to rhodium, and applied as a catalyst in the ACA of potassium vinyltrifluoroborate to cyclohexenone in a one-pot procedure with almost identical results compared to the use of a purified ligand. A combination of this cascade synthesis and catalysis with the automated parallel procedure, and in an ideal case also the multi-substrate method (Chapter 2) and the monodentate ligand combination approach (Chapter 5), would lead to a very rapid screening and optimization of phosphoramidite based catalysts.

## 7.9 Experimental section

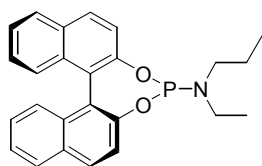
For general information see Chapters 2 and 4. For the library synthesis, reagent grade dried solvents were purchased from Fluka and used as received. Amines and enones were used as received; 2,3-dimethyl-2,3-dihydro-1H-indole, ethyl nipecotate, and perhydroisoquinoline were used as mixtures of stereoisomers. Dehydroamino acid **7.22** was kindly provided by Lavinia Panella. Synthesis and screening of the solution phase phosphoramidite ligand library was performed at DSM Pharma Chemicals under the guidance of Laurent Lefort and Jeroen Boogers. The library was synthesized using a Zinsser Lissy liquid handling robot

equipped with 4 probes and placed inside a glove box. Whatman PKP 2mL 96-well filter plates in combination with the UniVac 3 vacuum manifold were used to perform the parallel filtration of the ligand library. The reactions were carried out in a Premex 96-Multi Reactor that can accommodate 96 reactions vessels at the same temperature.

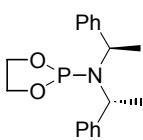
**General procedure A.** Preparative scale synthesis of phosphoramidite ligands via the phosphorochloridite, (*S*)-**L2**, (*R,R*)-**L4** and (*R,R*)-**L5**.



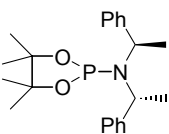
To a Schlenk vessel containing 3.0 g (10.5 mmol) of (*S*)-BINOL (**7.5**) was added 12 ml of  $\text{PCl}_3$ . The resulting suspension was refluxed overnight and excess  $\text{PCl}_3$  was removed in vacuo. Anhydrous toluene (3 x 5 ml) was added and the remaining  $\text{PCl}_3$  was removed by azeotropic distillation to give a white foam after thorough removal of all volatiles under high vacuum. The resulting phosphorochloridite **7.10** (3.6 g, 10.5 mmol, 100% yield,  $^1\text{H-NMR}$   $\delta$ : 8.01 (m, 4H), 7.56 (m, 8H);  $^{31}\text{P-NMR}$   $\delta$ : 177.6) was dissolved in 10.5 ml of anhydrous toluene and stored as a stock solution.



To 1.5 ml of a 1.0 M solution of **7.10** in toluene (1.5 mmol) was added 10 ml of anhydrous THF and the solution was cooled to 0 °C. Triethylamine (0.52 ml, 3.7 mmol) was added, followed by 0.2 ml (1.65 mmol) of *N*-ethylpropylamine (**7.11**), and the solution was stirred at 0 °C for 1h. Diethylether (10 ml) was added and the reaction mixture was filtered, concentrated under reduced pressure and purified by column chromatography (heptanes/ethyl acetate 8/1  $R_f$  0.7) to give 451 mg (1.1 mmol, 75%) of (*S*)-**L2** as a white foam after repetitive stripping with  $\text{CH}_2\text{Cl}_2$  at the rotatory evaporator. For spectral data see Chapter 6.



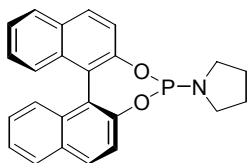
Starting from commercially available 2-chloro-1,3,2-dioxaphospholane, following the procedure described above, 519 mg (1.6 mmol, 55%) of (*R,R*)-**L4** was obtained as colorless crystals after purification by column chromatography (heptanes/ethyl acetate 6/1  $R_f$  0.6).  $^1\text{H-NMR}$   $\delta$ : 7.10 (m, 10H), 4.43 (m, 2H), 4.31 (m, 1H), 4.11 (m, 1H), 3.94 (m, 2H), 1.67 (d,  $J=7.2$  Hz, 6H);  $^{13}\text{C-NMR}$   $\delta$ : 143.1 (d,  $J=1.6$  Hz), 127.7, 127.6, 126.4, 64.0 (d,  $J=7.7$  Hz), 63.6 (d,  $J=8.5$  Hz), 52.5 (d,  $J=9.9$  Hz), 22.3 (d,  $J=9.9$  Hz);  $^{31}\text{P-NMR}$   $\delta$ : 143.2.  $[\alpha]_D^{25} = +228^\circ$  ( $c = 1.2$ ,  $\text{CHCl}_3$ ). MS (CI) 334  $[\text{M}+\text{NH}_4]^+$ . Anal. calcd for  $\text{C}_{18}\text{H}_{22}\text{NO}_2\text{P}$  C 68.56, H 7.03, N 4.44 found C 68.45, H 7.34, N 4.40. Mp 69°C.



Starting from commercially available 2-chloro-4,4,5,5-tetramethyl-1,3,2-dioxaphospholane, following the procedure described above, 551 mg (1.5 mmol, 50%) of (*R,R*)-**L5** was obtained as a colorless oil after purification by column chromatography (heptanes/ethyl acetate 10/1  $R_f$  0.6).  $^1\text{H-NMR}$   $\delta$ : 7.07 (m, 10H), 4.66 (m, 2H), 1.66 (d,  $J=7.2$  Hz, 6H), 1.38 (d,  $J=3.2$  Hz, 6H), 1.34 (d,  $J=5.2$  Hz, 6H);  $^{13}\text{C-NMR}$   $\delta$ : 143.4,

127.8, 127.6, 126.2, 81.1 (d,  $J = 4.6$  Hz), 51.5 (d,  $J = 10.6$  Hz), 26.3, 25.7, 25.6, 25.5;  $^{31}\text{P}$ -NMR  $\delta$ : 143.7.  $[\alpha]_{\text{D}}^{20} = +206^{\circ}$  ( $c = 1.3$ ,  $\text{CHCl}_3$ ). MS (CI) 334  $[\text{M} + \text{NH}_4]^+$ .

**General procedure B.** Preparative scale synthesis of phosphoramidite ligands via phosphorylation, (*S*)-L6.



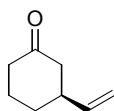
To a suspension of 286 mg (1.0 mmol) of (*S*)-BINOL (**7.5**) in 3 ml of anhydrous toluene was added 1 crystal of  $\text{NH}_4\text{Cl}$  followed by 321  $\mu\text{l}$  (1.4 mmol) of tris(1-pyrrolidinyl)-phosphine. The resulting clear solution was refluxed for 1 h after which the solvents were removed in vacuo. The residue was purified by column chromatography (heptanes/ethyl acetate 8/1  $R_f$  0.6) to give 233 mg (0.6 mmol, 61%) of (*S*)-L6 as a white foam after repetitive stripping with  $\text{CH}_2\text{Cl}_2$  at the rotatory evaporator. Spectral data were in accordance with literature.<sup>35</sup>

**General procedure C.** Synthesis of solution phase phosphoramidite ligand libraries.

Stock solutions were prepared by dissolving the proper amounts of every reagent necessary for the library synthesis in anhydrous toluene (all by weight). For the phosphorochloridites a concentration of 0.150 M was used, for the amines 0.157 M, and for the triethylamine 0.500 M. Using the liquid handling robot 0.333 ml (1.00 eq) of each of the three phosphorochloridite solutions was transferred into the corresponding 32 wells of the Whatman PKP filter plate. The triethylamine solution, 0.100 ml (1.00 eq), was added to each of the 96 wells. Next 0.333 ml (1.05 eq) of each of the 32 amine solutions was added to each of the three blocks of 32 wells. The microplate was placed on an orbital shaker and vortexed for 2 hours at room temperature. The microplate was then placed onto the vacuum manifold and filtration was performed upon application of vacuum. The filtrates, i.e. 96 solutions of different phosphoramidites in dry toluene (0.766 ml, 0.065M) were collected and stored into a 96-well polypropylene microplate.

**General procedure D.** Screening of solution phase phosphoramidite ligand libraries.

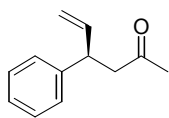
A stock solution containing the Rh precursor,  $\text{Rh}(\text{acac})(\text{eth})_2$  at a concentration of 0.0012 M, and the substrate, (**7.3**, **7.15** or **7.20**), at a concentration of 0.0310 M, in absolute ethanol was prepared. Using the liquid handling robot 0.100 ml (0.10 eq) of the 96 ligand solutions was transferred from the microplate into 96 vials, equipped with stirring bars. Then 2.0 ml of the  $\text{Rh}(\text{acac})(\text{eth})_2$  and substrate stock solution, (0.04 eq and 1.00 eq, respectively) was added to each of the 96 vials. After the addition of an estimated portion of 4 eq of organotrifluoroborate the vials were capped and transferred to the parallel reactor. The reactions were left stirring at reflux for the indicated time, and then analyzed by chiral GC in order to determine the conversion and the e.e.



**3-Vinyl-cyclohexanone (7.16).** According to general procedure **D**, for spectral and analytical data see Chapter 6. Enantiomer separation on a Chiraldex A-TA column, 30m x 0.25 mm x 0.12  $\mu$ m, 90°C isothermic, 11.8 / 12.4 min (GC). Quantitative data are given below (Table 7.3).

**Table 7.3** Conversions of 7.3 and e.e. values of 7.16.

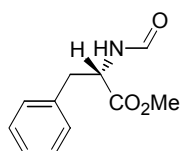
ligand (position)	conv. (%)	e.e. (%)	ligand (position)	conv. (%)	e.e. (%)	ligand (position)	conv. (%)	e.e. (%)
<b>1a</b>	19	79	<b>1e</b>	35	76	<b>1i</b>	4	16
<b>2a</b>	21	73	<b>2e</b>	53	78	<b>2i</b>	9	9
<b>3a</b>	34	64	<b>3e</b>	56	75	<b>3i</b>	6	7
<b>4a</b>	41	73	<b>4e</b>	62	72	<b>4i</b>	6	14
<b>5a</b>	10	18	<b>5e</b>	22	48	<b>5i</b>	24	25
<b>6a</b>	17	16	<b>6e</b>	21	14	<b>6i</b>	16	26
<b>7a</b>	12	41	<b>7e</b>	10	41	<b>7i</b>	12	40
<b>8a</b>	51	75	<b>8e</b>	80	82	<b>8i</b>	4	15
<b>1b</b>	52	84	<b>1f</b>	81	87	<b>1j</b>	4	14
<b>2b</b>	18	22	<b>2f</b>	21	14	<b>2j</b>	13	31
<b>3b</b>	12	19	<b>3f</b>	20	45	<b>3j</b>	22	27
<b>4b</b>	22	64	<b>4f</b>	62	77	<b>4j</b>	2	15
<b>5b</b>	12	21	<b>5f</b>	19	49	<b>5j</b>	23	27
<b>6b</b>	18	58	<b>6f</b>	20	75	<b>6j</b>	17	42
<b>7b</b>	14	44	<b>7f</b>	9	41	<b>7j</b>	19	37
<b>8b</b>	10	21	<b>8f</b>	17	48	<b>8j</b>	16	18
<b>1c</b>	10	34	<b>1g</b>	21	49	<b>1k</b>	7	22
<b>2c</b>	13	25	<b>2g</b>	20	45	<b>2k</b>	19	18
<b>3c</b>	45	67	<b>3g</b>	69	74	<b>3k</b>	4	6
<b>4c</b>	7	24	<b>4g</b>	19	43	<b>4k</b>	11	24
<b>5c</b>	31	31	<b>5g</b>	39	19	<b>5k</b>	21	50
<b>6c</b>	14	36	<b>6g</b>	7	53	<b>6k</b>	19	41
<b>7c</b>	15	33	<b>7g</b>	8	47	<b>7k</b>	10	41
<b>8c</b>	11	76	<b>8g</b>	22	82	<b>8k</b>	1	29
<b>1d</b>	13	11	<b>1h</b>	21	37	<b>1l</b>	12	14
<b>2d</b>	36	77	<b>2h</b>	74	78	<b>2l</b>	8	0
<b>3d</b>	22	52	<b>3h</b>	61	58	<b>3l</b>	3	15
<b>4d</b>	35	82	<b>4h</b>	41	72	<b>4l</b>	8	4
<b>5d</b>	7	28	<b>5h</b>	5	28	<b>5l</b>	8	25
<b>6d</b>	9	26	<b>6h</b>	13	37	<b>6l</b>	24	39
<b>7d</b>	13	49	<b>7h</b>	10	47	<b>7l</b>	14	40
<b>8d</b>	17	37	<b>8h</b>	17	42	<b>8l</b>	11	14



**4-Phenyl-hex-5-en-2-one (7.18).** According to general procedure **D**, spectral data were in accordance with literature.<sup>36</sup> Enantiomer separation on a Chiraldex G-TA column, 30m x 0.25 mm x 0.25  $\mu$ m, 125°C isothermic, 11.2 / 11.5 min (GC). Quantitative data are given below (Table 7.4).

**Table 7.4** Conversions of 7.17 and e.e. values of 7.18.

ligand (position)	conv. (%)	e.e. (%)	ligand (position)	conv. (%)	e.e. (%)	ligand (position)	conv. (%)	e.e. (%)
<b>1a</b>	69	10	<b>1e</b>	92	7	<b>1i</b>	14	10
<b>2a</b>	82	22	<b>2e</b>	84	15	<b>2i</b>	17	12
<b>3a</b>	92	31	<b>3e</b>	88	33	<b>3i</b>	13	4
<b>4a</b>	99	23	<b>4e</b>	96	21	<b>4i</b>	20	13
<b>5a</b>	1	0	<b>5e</b>	6	25	<b>5i</b>	10	9
<b>6a</b>	16	34	<b>6e</b>	42	28	<b>6i</b>	8	6
<b>7a</b>	35	21	<b>7e</b>	52	24	<b>7i</b>	16	5
<b>8a</b>	99	17	<b>8e</b>	96	8	<b>8i</b>	17	4
<b>1b</b>	99	8	<b>1f</b>	88	3	<b>1j</b>	15	5
<b>2b</b>	28	24	<b>2f</b>	49	29	<b>2j</b>	9	6
<b>3b</b>	6	12	<b>3f</b>	1	25	<b>3j</b>	9	10
<b>4b</b>	77	40	<b>4f</b>	99	30	<b>4j</b>	11	4
<b>5b</b>	15	35	<b>5f</b>	26	26	<b>5j</b>	10	10
<b>6b</b>	31	37	<b>6f</b>	24	23	<b>6j</b>	8	4
<b>7b</b>	38	18	<b>7f</b>	35	19	<b>7j</b>	13	7
<b>8b</b>	28	32	<b>8f</b>	44	27	<b>8j</b>	13	10
<b>1c</b>	22	43	<b>1g</b>	49	34	<b>1k</b>	4	5
<b>2c</b>	21	36	<b>2g</b>	2	28	<b>2k</b>	16	11
<b>3c</b>	78	37	<b>3g</b>	99	25	<b>3k</b>	16	4
<b>4c</b>	12	41	<b>4g</b>	16	27	<b>4k</b>	10	9
<b>5c</b>	35	32	<b>5g</b>	49	31	<b>5k</b>	14	6
<b>6c</b>	32	28	<b>6g</b>	36	29	<b>6k</b>	19	7
<b>7c</b>	33	16	<b>7g</b>	40	21	<b>7k</b>	17	5
<b>8c</b>	63	30	<b>8g</b>	83	22	<b>8k</b>	3	8
<b>1d</b>	22	30	<b>1h</b>	13	30	<b>1l</b>	6	10
<b>2d</b>	91	14	<b>2h</b>	99	24	<b>2l</b>	16	15
<b>3d</b>	89	42	<b>3h</b>	99	40	<b>3l</b>	11	24
<b>4d</b>	70	2	<b>4h</b>	99	17	<b>4l</b>	22	29
<b>5d</b>	15	22	<b>5h</b>	36	26	<b>5l</b>	21	8
<b>6d</b>	34	32	<b>6h</b>	52	26	<b>6l</b>	12	3
<b>7d</b>	30	25	<b>7h</b>	70	23	<b>7l</b>	16	4
<b>8d</b>	45	33	<b>8h</b>	37	31	<b>8l</b>	16	8



**2-Formylamino-3-phenyl-propionic acid methyl ester (7.24).** According to general procedure **D**, spectral data were in accordance with literature.<sup>37</sup> Enantiomer separation on a Chirasil L-Val column, 30m x 0.25 mm x 0.12  $\mu$ m, 120°C 8 min, then 10°C/min to 150°C, 17.9 / 18.7 min (GC). Quantitative data are given below (Table 7.5).

**Table 7.5** Conversions of 7.22 and e.e. values of 7.24.

ligand (position)	conv. (%)	e.e. (%)	ligand (position)	conv. (%)	e.e. (%)	ligand (position)	conv. (%)	e.e. (%)
1a	11	2	1e	12	16	1i	7	4
2a	44	10	2e	28	16	2i	7	6
3a	13	12	3e	10	12	3i	6	3
4a	28	8	4e	24	20	4i	6	7
5a	13	1	5e	17	2	5i	30	16
6a	32	4	6e	32	18	6i	35	17
7a	31	8	7e	20	9	7i	13	2
8a	55	19	8e	38	23	8i	8	7
1b	64	28	1f	43	24	1j	7	13
2b	40	15	2f	51	25	2j	21	16
3b	16	1	3f	4	8	3j	22	12
4b	29	14	4f	45	35	4j	5	9
5b	22	3	5f	20	15	5j	24	17
6b	13	0	6f	11	12	6j	9	2
7b	24	3	7f	19	3	7j	17	1
8b	33	10	8f	29	15	8j	25	13
1c	29	5	1g	23	16	1k	22	14
2c	40	6	2g	7	2	2k	30	14
3c	23	10	3g	48	24	3k	7	0
4c	12	1	4g	12	8	4k	24	11
5c	48	10	5g	40	17	5k	14	5
6c	23	6	6g	26	6	6k	17	6
7c	17	3	7g	23	7	7k	16	9
8c	15	9	8g	26	34	8k	3	1
1d	37	2	1h	20	14	1l	0	0
2d	52	26	2h	74	38	2l	8	7
3d	35	24	3h	58	32	3l	4	2
4d	24	10	4h	50	27	4l	7	10
5d	3	7	5h	1	20	5l	7	13
6d	17	1	6h	27	6	6l	21	14
7d	14	6	7h	31	14	7l	16	8
8d	20	8	8h	22	11	8l	13	7

**General procedure E.** Cascade synthesis and catalysis.

To a flame dried Schlenk tube flushed with nitrogen, 25  $\mu\text{l}$  (0.025 mmol, 1.0M in toluene) of phosphorochloridite **7.23** was added followed by 50  $\mu\text{l}$  (0.025 mmol, 0.5M in toluene) of  $\text{Et}_3\text{N}$  and 25  $\mu\text{l}$  (0.025 mmol, 1.0M in toluene) of diethylamine (**7.24**). The resulting turbid mixture was stirred at room temperature for 1h after which 2.0 ml of an absolute ethanol stock solution containing 25  $\mu\text{l}$  (0.25 mmol) of **7.3**, 2.6 mg (0.01 mmol) of  $\text{Rh}(\text{acac})(\text{eth})_2$  and 5  $\mu\text{l}$  of n-tridecane (GC internal standard) was added. After the addition of 134 mg (1.0 mmol) of **7.15** the resulting mixture was heated at reflux for 3h, and subsequently analyzed by chiral GC (see Chapter 6 for details).

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