Summary

This thesis describes the development of strategies for the introduction of phosphine ligands into DNA. Covalent and non-covalent anchoring processes have been explored. Where possible the developed systems were applied in asymmetric transition metal catalysed reactions. These catalytic reactions have been optimised under DNA compatible conditions. The goal of this research is 1) to find out to what extent metal catalysed systems are compatible with DNA technology and 2) to investigate if DNA is able to direct the selectivity of metal catalysed reaction.

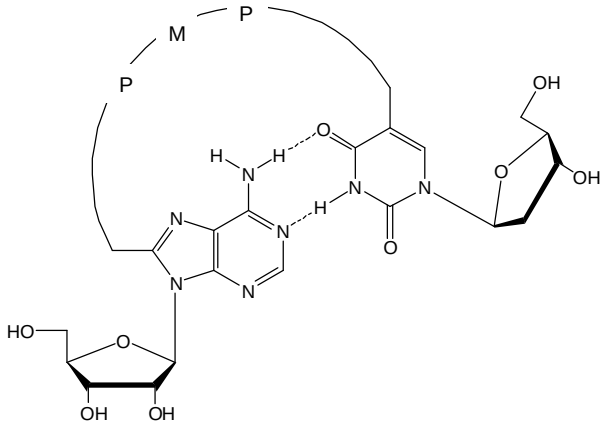


Figure 1: Schematic representation of ligand design described in *Chapter 2*.

In *Chapter 2* the functionalisation of mononucleotides with mono- and bidentate phosphine ligands was reported. These ligands were evaluated in different asymmetric catalytic reactions to investigate if there was any chiral induction resulting from the single nucleotides. Also, combinations were made between monodentate phosphine functionalised adenosine and thymidine, Figure 1. The sugar moiety is the chiral auxiliary, but quite far away from the transition metal centre. As mentioned in Chapter 1, it is known that secondary interactions between the ligand and the substrate can affect the chiral induction. In Chapter 2 important control experiments for the application of longer, phosphine-modified, oligonucleotides were described.

New mono- and bidentate phosphine ligands with adenosine as auxiliary were synthesized successfully, respectively ligands **A** and **E** and **F**. The monodentate ligand **A** was combined with three monodentate phosphine ligands with a thymidine auxiliary (ligands **B**, **C** and **D**) to create a mixed donor system in the asymmetric rhodium catalysed hydrogenation and palladium catalysed substitution reactions. In both reactions no or low enantiomeric excess was obtained. Also with the use of the bidentate ligands **E** and **F** no enantiomeric excess was

induced in the catalytic reactions. Conversions were high for all reactions except for the hydrogenation of dimethyl itaconate with the monodentate ligand combinations. For these reactions conversions around 20% were obtained.

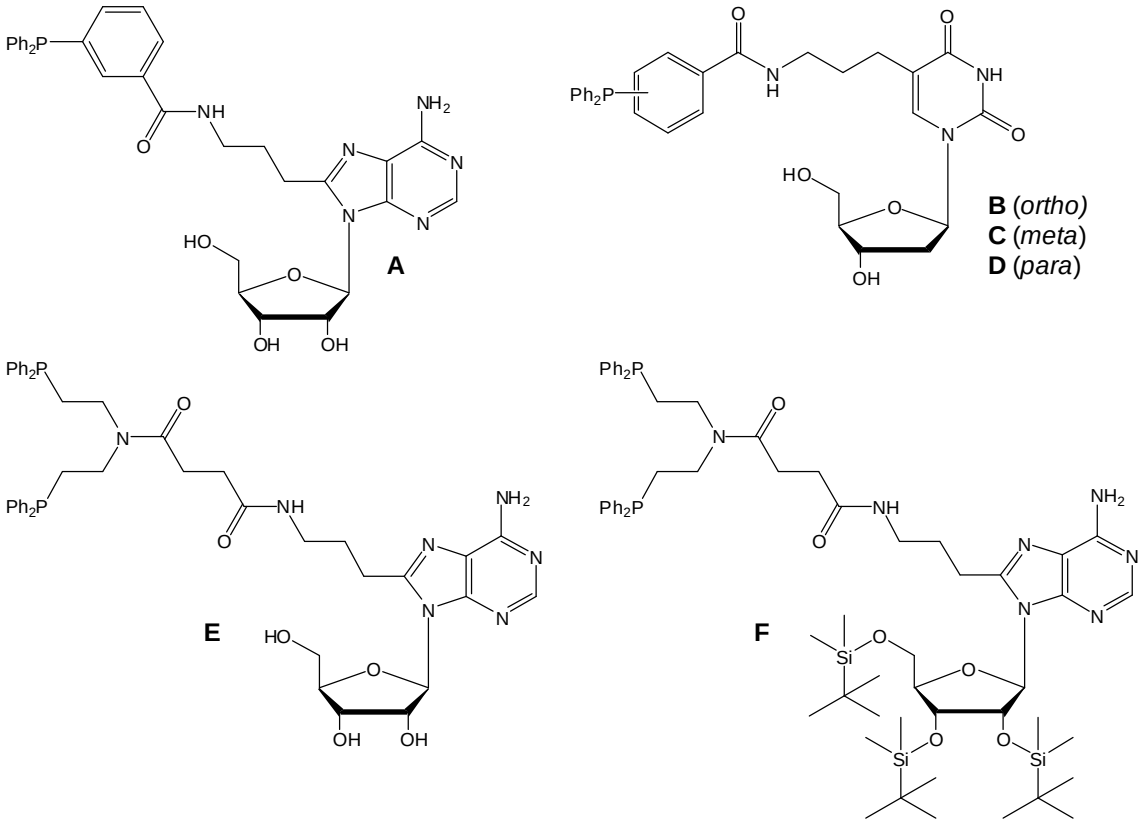


Figure 2: Nucleoside based mono- and bidentate phosphine ligands.

These results are good control experiments for the application of longer phosphine modified oligonucleotides. If in the catalytic reactions with these longer phosphine modified oligonucleotides enantiomeric excess will be obtained, most likely this can attributed to the chiral helix of DNA, because monoadenosine ligands did not give rise to enantiomeric excesses.

The covalent approach is described in *Chapter 3*. A post-synthetic method was developed for the functionalisation of a 9- and 15-mer with phosphine ligands. Adenosine was used as DNA building block and functionalised with a phosphine auxiliary. Recently our group published the method for the functionalisation of thymidine with phosphine ligands as DNA building block.

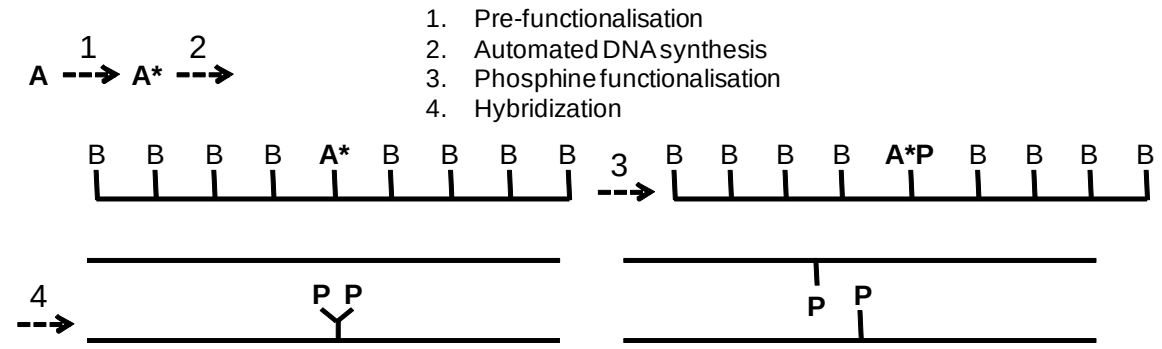


Figure 3: Schematic representation of the order of synthesis and functionalisation described in *Chapter 3*.

We have chosen for a strategy in which the phosphine ligand is coupled in the final step of the synthesis scheme, because of the incompatibility of phosphines with the automated DNA synthesis; in addition it gives us the possibility to introduce various mono- and bidentate ligands into the same strand, Figure 3.

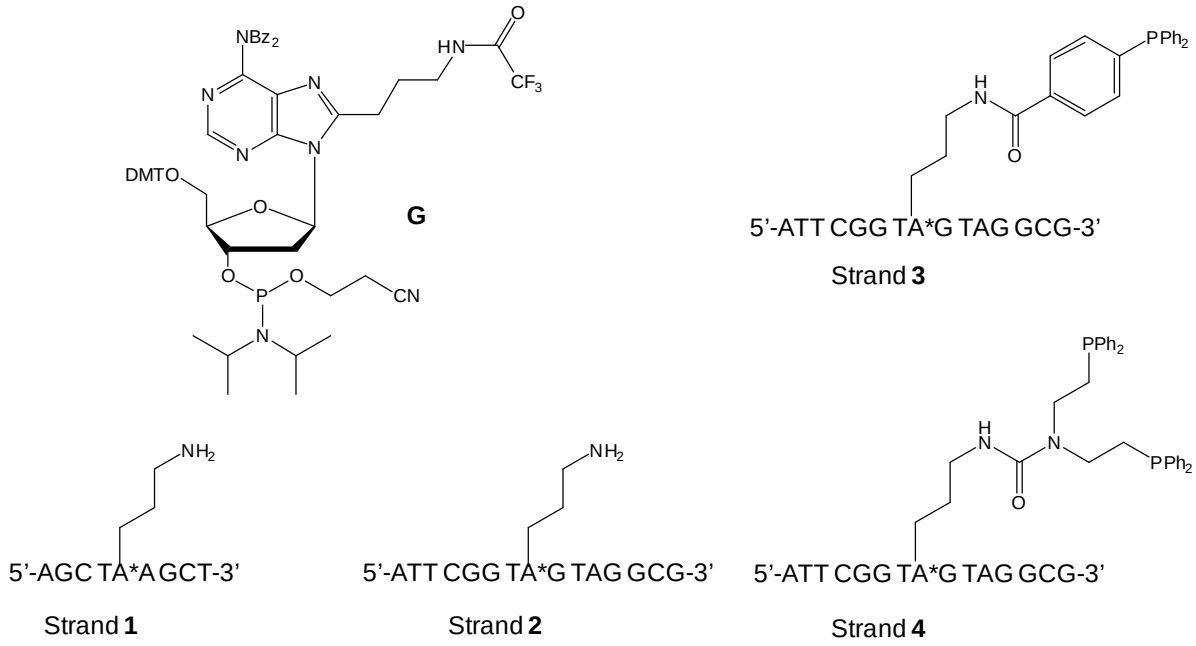


Figure 4: In Chapter 3 building block **G** was synthesised and incorporated into 9- and 15-mer **1** and **2**. Strand **2** was functionalised with a mono- and bidentate phosphine ligand.

From Chapter 3 could be concluded that we were able to prepare building block **G**, suitable for automated DNA synthesis starting from commercially available 8-bromoadenosine. In nine steps this adenosine was functionalised with a protected amine, the 2'-OH group was removed and the 3'- and 5'-OH groups were protected and converted to a suitable coupling moiety. This building block **G** was successfully incorporated in a 9- and 15-mer, strand **1** and **2**. Functionalisation with a monodentate and bidentate phosphine ligand was also successfully performed, but strands **3** and **4** could not be isolated in the non-oxidised phosphine form. It

can be concluded that the excesses (~500 equivalents) of organic reactants/reagents can be removed completely by washing with dichloromethane followed by ethanol purification or by using a NAP-10 column. Thus it is indeed possible to functionalise oligonucleotides with phosphine ligands, but the procedure should be further optimized to obtain the pure phosphine rather than phosphine oxide.

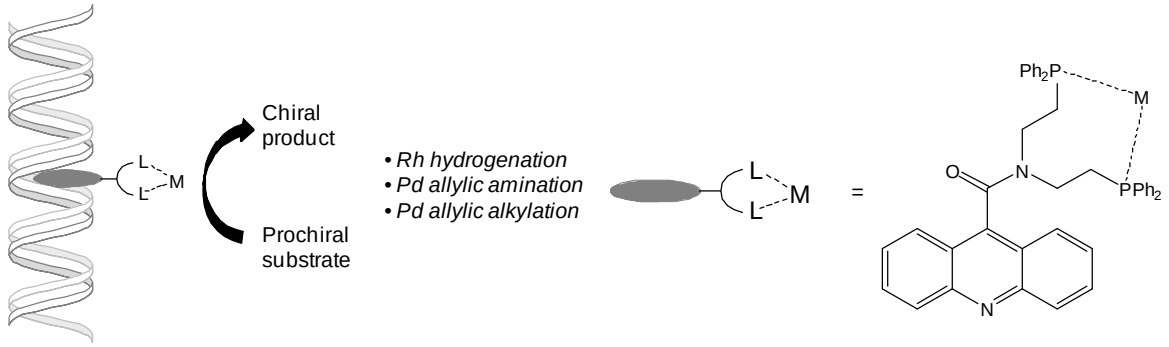
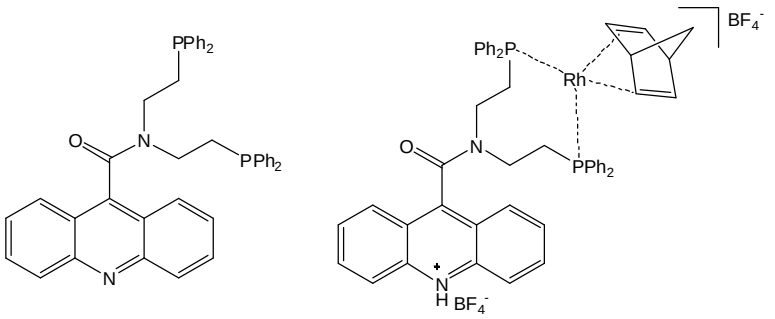


Figure 5: Schematic representation of ligand design and non-covalent anchoring to DNA described in *Chapter 4* (Rh hydrogenation) and *Chapter 5* (Pd allylic amination and alkylation).

In *Chapter 4* and *Chapter 5* a non-covalent introduction of phosphine ligands to DNA was described. Acridine was functionalised with a bidentate phosphine ligand. The obtained ligand contains three key structural features: a DNA intercalating moiety (acridine), a spacer and a metal-binding group (bidentate phosphine). This newly designed ligand was applied in rhodium catalysed hydrogenation reactions (*Chapter 4*) and palladium catalysed allylic asymmetric amination and alkylation reactions (*Chapter 5*). DNA compatible conditions were developed for these asymmetric catalytic reactions. The metal complexes are achiral and DNA is used as the sole chiral source, Figure 5. The main questions to be addressed are if there is a compatibility window and if the chirality can be transferred from the DNA to the metal complex in such manner that the assembly functions as a chiral catalyst.



H **I**

Figure 6: Phosphine ligand **H** of Chapter 4 and 5. Complex **I** was synthesised and characterised in Chapter 4.

An acridine was successfully functionalised with a bidentate phosphine ligand, **H**. From Chapter 4 can be concluded that the complexation of ligand **H** to $[Rh(nbd)_2]BF_4$ is not straightforward and the reaction conditions had to be optimised to obtain pure complex **I**. Complex **I** was analysed with different techniques and its solid state structure was confirmed by X-ray analysis. Rh complex **I** performed very well in the hydrogenation of methyl acetamidoacrylate under DNA compatible conditions, but unfortunately not in the presence of *Salmon Testes* DNA or a synthetic oligonucleotide. CD spectroscopy experiments showed a change in the region of the DNA upon addition of complex **I**, but there is no CD signal observed in the area in which the metal complex absorbs. This suggests that the chirality of the DNA is not transmitted to the metal-complex. More detailed experiments with the synthetic oligonucleotide are required to fully understand the properties of DNA-complex interactions and its translation to the rhodium hydrogenation, resulting so far in a decrease in activity.

From the palladium-catalyzed allylic alkylation reactions, described in Chapter 5, it can be concluded that the complex formed *in situ* by the palladium allyl chloride dimer and the diphosphinoacridine ligand **H** are active, but should be used directly after preparation and it is better not to incubate overnight in a mixture of water and DMF (10%). The *st*DNA has definitely an influence on the activity of the catalyst, because the conversions are much lower in the presence of *st*DNA and only 20% conversion was reached. In none of the experiments an enantiomeric excess was obtained. Future experiments could include to perform the reaction at lower temperature or using other sources of DNA, for instance also smaller (synthetic) strands.

The palladium ligand **H** system is more active in the allylic amination reaction than in the reaction with malonate and full conversion could be obtained without incubation. Still, in the presence of *st*DNA no enantioselectivity was obtained. The circular dichroism experiments suggest that there is interaction of the palladium complex with the *st*DNA, as the CD intensity of the *st*DNA decreases. There is no CD effect in the window where only the Pd-complex absorbs, providing no proof for the transfer of chirality from the DNA to the metal complex.