SUMMARY

The work described in this thesis was performed as part of a project aimed at the development of new homogeneous catalysts for the production of fine-chemicals, sponsored by DSM and the EET programme (Ecology, Economy and Technology) of the Netherlands Ministry of Economic Affairs. In the studies presented here, we focused on palladium-catalysed cross-coupling reactions and related procedures that result in the formation of new carbon-carbon bonds. These catalytic conversions are among the most versatile and important reactions for the construction of new, valuable molecules from simple building blocks. The results from this research will be briefly summarised below.

Bidentate diphosphine ligands are among the most widely applied ligands in many transition-metal catalysed carbon-carbon bond formation reactions. Large bite angle diphosphines based on xanthene-type backbones were tested as auxiliaries in several palladium and nickel-catalysed cross-coupling reactions, as described in *Chapter 2.* To gain mechanistic insight, a series of (P-P)Pd(4-C_6H_4CN)(X) (P-P = xanthene-based diphosphine, X = Br, CF_3SO_3) has been prepared and characterised in both the solid state and in solution. These complexes can a priori be envisaged as important intermediates in cross-coupling reactions. Despite the fact that the ligands differ only slightly in the magnitude of their natural bite angle, large variations were observed in the coordination behaviour of the diphosphines in the palladium(II)-complexes. An unexpected *trans* coordination, with P-Pd-P angles ranging from 150-165°, was found for the Xantphos-type ligands, as determined by X-ray analysis and NMR spectroscopy. In solution, these *trans* complexes are in exchange with their *cis* isomers. DPEphos adopts a *cis* chelation mode, both in the solid state and in solution. The large differences in coordination mode appeared to have a dramatic influence on the reaction rate and selectivity in the palladium-catalysed Kumada coupling between bromobenzene and alkyl Grignard reagents. The observed trends can be explained by the relative rates of the competitive reductive elimination and β-H elimination from the intermediate *cis* and *trans* Pd(aryl)(alkyl) complexes. In contrast, in the Heck reaction no clear bite angle trend could be observed. It is proposed that in the Heck reaction the (P-P)Pd(4-C_6H_4CN)(X) complexes are not the actual intermediates in the catalytic cycle, but undergo transformation of the diphosphine to a monodentate species before the catalysts gain activity. This process is likely to occur through phosphonium salt formation or phosphine oxidation.

Since from Chapter 2 it was concluded that diphosphines in general do not give rise to very effective catalysts for Heck couplings, we turned to monodentate ligands. This is described in

Chapter 3. From initial screening experiments it was found that application of bulky monodentate phosphoramidite ligands results in highly active palladium catalysts for the Heck reaction of aryl iodides with alkenes under mild conditions. This class of ligands provides the optimum steric and electronic properties for fast reaction within the series tested. The steric bulk of the ligand, which enforces mono-coordination, plays an important role herein. Various aryl iodides and aryl bromides can be coupled efficiently with electron-poor alkenes under mild conditions in aprotic, polar solvents. The dinuclear complex $[Pd(L)(Ph)(\mu\text{-}Br)]_2$ (L = *N,N*-diisopropylamino-2,2'-di-*tert*-butyl-4,4'-dimethoxybisphenoxy phosphite) was isolated and characterised and shown to be an intermediate in the catalytic cycle. Kinetic studies showed that using this complex as the catalyst the reaction rate is proportional to the styrene concentration and the square root of the palladium concentration. These results are interpreted in terms of a mechanism in which the dimeric complex functions as the resting state of the catalyst. This dimer is in rapid equilibrium with its monomeric form, which is present in very low concentrations. In the subsequent step of the catalytic cycle, the monomer reacts with the alkene. From the electronic dependence of the substrates on the reaction rate it is proposed that the migratory insertion of the alkene into the Pd(aryl) bond is the slow step of the catalytic cycle.

The discovery that application of bulky monodentate phosphoramidites as ligands results in very active Heck catalysts prompted us to extend our studies into the field of *asymmetric* Heck reactions. In *Chapter 4*, the comparison of a series of chiral phosphoramidites based on different backbones in the intramolecular Heck cyclisation towards spirooxindoles is described. It appeared that TADDOL-based phosphoramidites can give rise to very fast reaction under mild conditions in enantioselectivities of up to 79 % (when using (1*R*,7*R*)-4-Diethylamino-9,9-dimethyl-2,2,6,6-tetra(3,5-dimethylphenyl)-3,5,8,10-tetraoxa-4-phosphabicyclo[5.3.0]decane). Bidentate ligands often require much longer reaction times and higher temperatures to reach good conversion. A palladium(aryl)(halide) complex containing a chiral phosphoramidite was isolated and it was shown to exist mainly as a dimer during catalysis in solution and the solid state. From the observed trend in selectivity it followed that a kinetic resolution mechanism is probably involved. In this mechanism, one of the enantiomers initially formed after the insertion of the alkene into the Pd(aryl) bond undergoes faster dissociation from the metal centre to give the product than the opposite enantiomer. The latter enantiomer is more prone to re-insert into the transient palladium hydride species and thereby form the isomer of the alkene.

The same series of chiral phosphoramidites was also tested in another important palladium-catalysed cross-coupling reaction: the asymmetric Suzuki coupling of naphthyl substrates to give axially chiral binaphthyls. As described in *Chapter 5*, these catalytic reactions also proceed smoothly under mild conditions (room temperature), even with naphthyl bromides. The influence of the solvent and base was investigated and under optimised conditions enantioselectivities of 63 % were obtained.

A different important carbon-carbon bond formation reaction was selected as the subject of our studies in *Chapter 6*. The palladium-catalysed allylic alkylation reaction using soft carbon nucleophiles and bulky phosphoramidites as the ligand was investigated. It was found that the observed regioselectivity depends strongly on the leaving group and the geometry of the allylic substrates. Complex studies revealed that also in the case of Pd(allyl)(X) complexes mono-coordination of the phosphoramidites occurs. The allyl fragment is bonded in a non-symmetric way in these complexes, caused by the difference in *trans* influence of the other ligands. Upon employing mono-substituted allyl substrates, the *syn*, *trans* complexes are the main species present in solution. This complex, however, undergoes fast isomerisation towards the more reactive *syn*, *cis* complexes, resulting in the formation of linear product as the major product. However, in the case of bulky biphenol or BINOL-based phosphoramidites a strong memory effect is observed when 1-phenyl-2-propenyl acetate is employed as the substrate. In this situation, isomerisation is relatively retarded with respect to nucleophilic attack. The asymmetric allylic alkylation of 1,3-diphenyl-2-propenyl acetate using chiral bulky monodentate phosphoramidites afforded the corresponding chiral product in enantioselectivities of up to 93 % ee. Substrates with smaller substituents resulted in lower ee's. These observations can be rationalised in terms of a preferential rotation mechanism, in which the product is formed by attack on one of the possible intermediate Pd(allyl) complexes.

Concluding, it was demonstrated in this and the preceeding chapters that bulky monodentate phosphoramidites form a new, promising class of ligands for palladium-catalysed C-C bond formation reactions under mild conditions. Their synthesis is relatively simple and allows a modular approach, thereby enabling a systematic ligand optimisation for a given reaction. We expect that these properties make phosphoramidites attractive candidates for future applications in these and other metal-catalysed reactions.

The development of palladium-catalysed coupling procedures that do not produce a stoichiomeric amount of salt waste is highly desirable, especially from an environmental point of view. Therefore, we studied the feasibility of Heck-type coupling reactions that occur through a C-H bond activation mechanism, as described in *Chapter 7*. From parallel screening experiments we found that anilide derivatives can be coupled efficiently with electron-poor alkenes using $Pd(OAc)_2$ as the catalyst in the presence of an oxidant. The reaction proceeds in an acidic environment under mild conditions. The amide functionality directs the reaction to proceed *via* activation of the *ortho* C-H bond. Electron-rich aromatic compounds react faster than substrates bearing electron-withdrawing substrates. The reaction exhibits first order kinetics in acetanilide and a small kinetic isotope effect ($k_H/k_D = 3$). Based on these observations we propose a mechanism in which electrophilic attack of the palladium complex on the π-system of the anilide takes place, followed by deprotonation of the resulting complex. In this sequence the former step is likely to be relatively slow. At slightly elevated temperatures, molecular oxygen can be applied as the oxidant, resulting in a reaction that produces only water as the side-product. This type of catalytic conversions brings waste-free coupling reactions a step closer.