1.1 Introduction

1.1.1 P-Stereogenic Ligands in Asymmetric Catalysis

1.1.1.1 Chirality at Phosphorus Atoms

Identical to a sp^3 hybridized carbon, trivalent and tetravalent phosphorus compounds adopt a tetrahedral geometry. Depending on the substitution pattern this can result in the formation of a stereogenic center. In trivalent phosphorus species the free electron pair is counted as a substituent and, unlike the corresponding nitrogen compounds, their geometry is configurationally stable and does not undergo inversion under ambient conditions. The inversion barrier of phosphines is generally 125-145 kJ/mol.[1] For example, PH_3 has an inversion barrier of 132 kJ/mol compared to 24 kJ/mol for NH_3.[2]

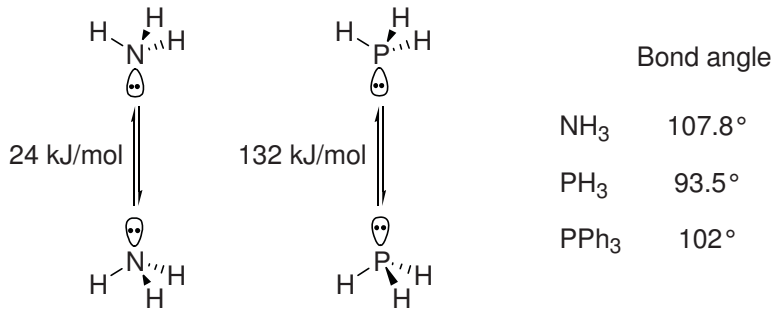


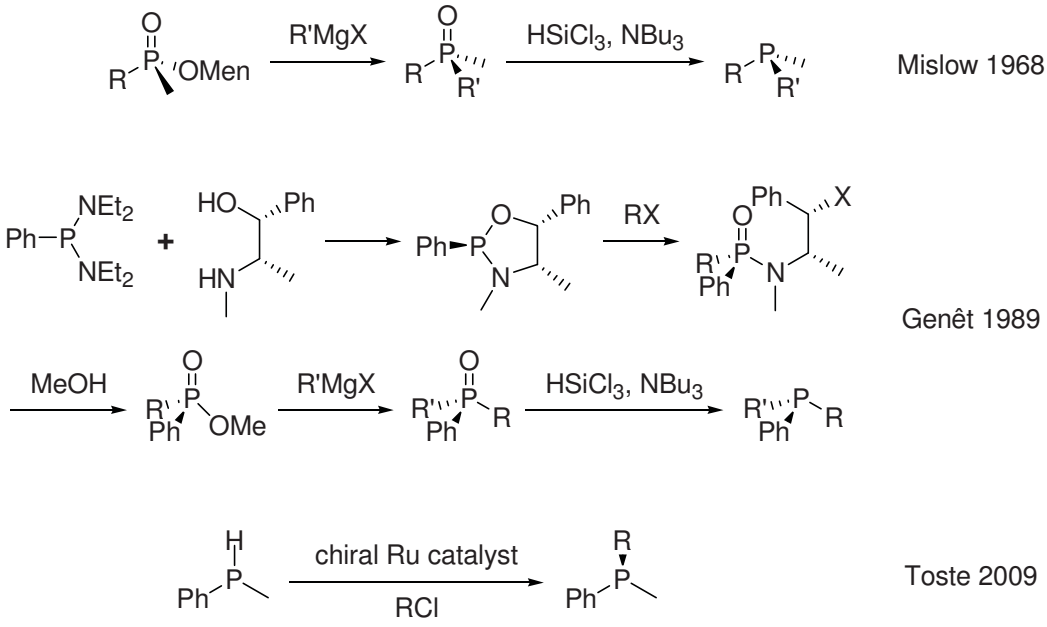
Figure 1.1. Physical properties of phosphines.

The increased energy requirement for the phosphorus inversion follows from the enhanced geometrical distortion necessary to form the trigonal planar transition state. Larger bonding angles need less distortion than smaller bonding angles. The bond angles in trivalent phosphorus compounds are smaller than those of trivalent nitrogen or tetravalent carbon species. This can be explained as a result of endothermic hybridization energy combined with VSEPR-theory.[3] Whereas the electron distribution favours a geometry with orthogonal orbitals (bonding angle of 90°), VSEPR-theory, based on electron-electron repulsion, predicts an alignment close to the geometry of a tetrahedron. The two effects oppose each other and the outcome is a compromise, as seen in the numbers of Figure 1.1.

1.1.1.2 Preparation of P-Stereogenic Phosphines

Preparation of enantiomerically pure chiral phosphines dates back to the 1960's when the groups of *Horner* and *Mislow* were studying the stereochemistry of substitution reactions on phosphorus compounds. In the beginning, the phosphines were prepared by electrochemical reduction of optically pure phosphonium compounds which had been resolved by fractional crystallization.[4a] Later, a synthesis was developed consisting of the resolution of menthyl phosphinates followed by addition of a *Grignard*-reagent and reduction of the resulting phosphine oxides (Scheme 1.1).[4b] Later, *Knowles'* P-stereogenic diphosphine ligand DIPAMP was synthesized by oxidative coupling of two phosphines.[5]

Twenty years passed before *Jugé* and *Genêt* described a new methodology that avoided chiral resolution. The synthetic route consisted of the diastereoselective formation of chiral oxazaphospholidines and the subsequent displacement by aryl or alkyl halides (Scheme 1.1).[6a] The group of *Corey* also published a similar procedure using oxathiaphospholidines.[6b]



Scheme 1.1. Stereoselective syntheses of chiral phosphines.

Despite these advances, the stereoselective preparation of acyclic chiral phosphines has remained a rather undeveloped area. Since they are mostly used as ligands in transition metal catalyzed reactions, the success of ligands with a chiral backbone instead of a chiral

phosphorus did not encourage reasearchers to develop new synthetic methodologies to overcome the tedious preparation of chiral phosphines. Only recently have new efforts, using catalysis, been seen.[7] By employing chiral Pd-,[8a] Pt-[8b] or Ru-catalysts[8c,d] enantioselective hydrophosphination and alkylation reactions have been achieved by several research groups.

1.1.1.3 Transition Metal-Catalyzed Asymmetric Hydrogenation of Functionalized Olefines

In 1965 *Wilkinson* found a practical rhodium-catalyst for homogeneous hydrogenation (Figure 1.2).[9] Based on the finding that chiral trivalent phosphorus compounds can exist as stable, non-interconverting enantiomers by *Mislow* and *Horner*,[10] *Knowles* was able to demonstrate in 1968 the first asymmetric hydrogenation shortly before *Horner*.[11] The discovery of bidentate phosphines with chirality on the ligand backbone instead on the phosphorus as effective ligands by *Kagan*[12] and the development of an industrial scale asymmetric hydrogenation of *L*-DOPA at Monsanto[13] established this type of reaction in organic chemistry.

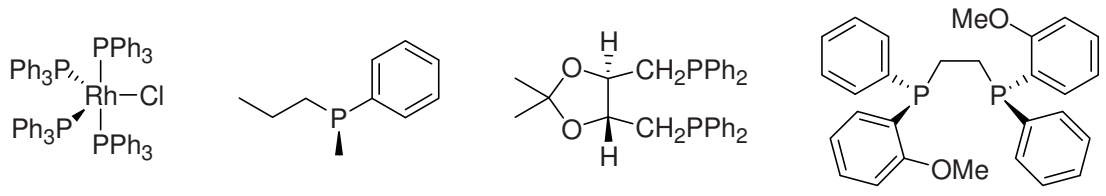
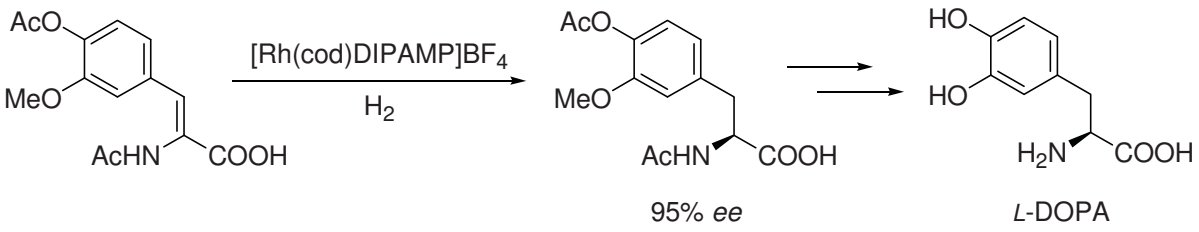
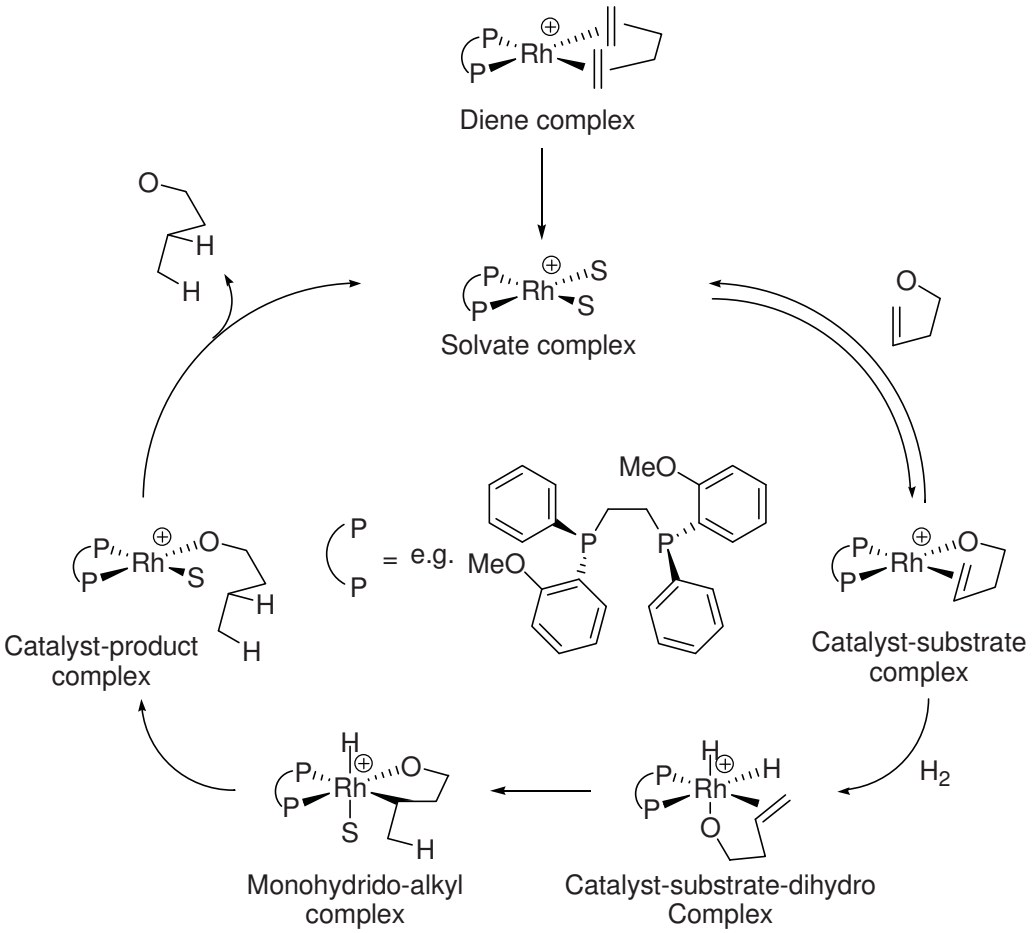


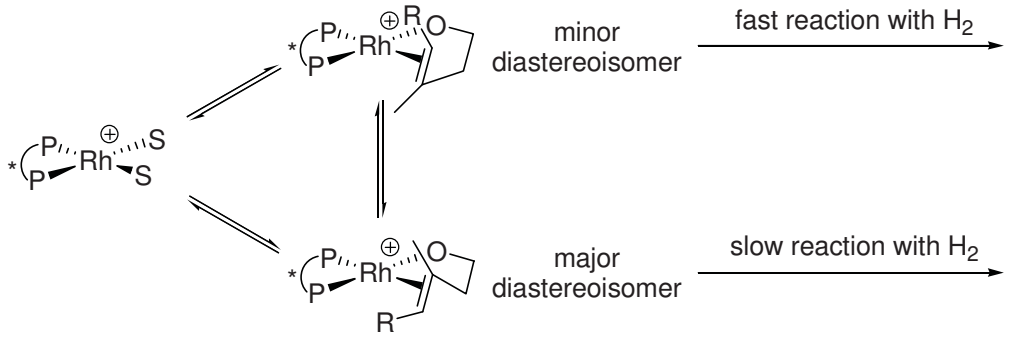
Figure 1.2. Early sytems in Rh-catalyzed hydrogenation.



Scheme 1.2. Rh-catalyzed hydrogenation in the *L*-DOPA synthesis at Monsanto.



Scheme 1.3. Unsaturated pathway of the Rh-catalyzed hydrogenation



Scheme 1.4. Interconversion of the diastereomeric catalyst-substrate complexes.

The mechanism of Rh-catalyzed asymmetric hydrogenation has been extensively studied.[14] Analyses of kinetic data[15] and characterization of reaction intermediates by NMR[16] or X-ray crystallography[17] provided insight into the catalytic cycle depicted in Scheme 1.3. The cationic bisphosphine-rhodium complex exists in methanol as a bis-solvate species with a low affinity towards dihydrogen. In the presence of the substrate, bidentate complexation occurs to form the catalyst-substrate complex. Addition of dihydrogen is rate-limiting and the subsequent migratory insertion gives the monohydrido-alkyl complex. The intermediate catalyst-substrate-dihydrido complex is assumed but has never been observed. Reductive elimination and dissociation of the hydrogenation product regenerates the catalyst and closes the cycle (Scheme 1.3).

For C_2-symmetrical chiral diphosphine ligands the catalyst-substrate complex exists as two interconverting diastereoisomers (Scheme 1.4). The interconversion can take place intramolecularly or via the solvate complex, the latter being less important. Usually one diastereoisomeric catalyst-substrate complex is more abundant in the equilibrium but, at least in the catalytic cycle shown above, this major diastereoisomer does not lead to the preferred hydrogenation product. The minor diastereoisomer reacts faster with dihydrogen to give the monohydrido-alkyl complex and therefore determines the stereochemical outcome of the reaction.

With the development of new bis-phosphine ligands the catalytic cycle was further investigated, and especially for electron rich phosphine donors, a slightly different pathway was found (Scheme 1.5).[18] Reversible formation of the catalyst-solvate-dihydro complex, whose diastereoisomers exist in equilibrium, is the first step. This dihydride reacts with the substrate to give the monohydrido-alkyl complex as the next detectable intermediate. The product is liberated after reductive elimination.