Summary

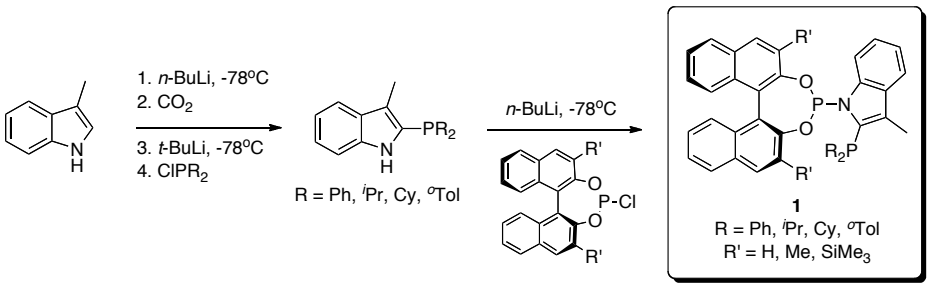
Indole-based phosphorus ligands in asymmetric catalysis

Over the last decades, catalysis has brought about a silent revolution in organic synthesis that rapidly spilled over to the industrial manufacturing of bulk and fine chemicals and pharmaceuticals. In a sustainable society in which waste streams need to be minimized but profits cannot be compromised, catalysis plays a pivotal role, as it enables selective conversions solely towards the desired product. However, to arrive at such selective processes is no easy task. A number of challenges, in particular for catalytic enantioselective transformations, appear as obstacles on the road towards new catalysts and processes, such as the specificity of catalysts for only a very limited number of substrates, the often long and laborious synthesis of catalysts and ligands, and elaborate catalyst evaluation. In this thesis several approaches are presented that address these challenges. The development of chiral hybrid bidentate IndolPhos ligands that provide highly efficient catalysts (chapters 2-7), a novel catalyst selection tool (chapter 8), and an unprecedented mode of dihydrogen activation (chapter 9) all contribute to more selective and sustainable processes in chemical manufacturing. Indole plays an important role in all these applications as structural basis of the novel ligands that enable the newly developed technologies.

With over three thousand chiral phosphorus ligands known, some of which are reviewed in chapter 1, a useful contribution to this area of research requires a thorough ligand design rationale. In order to ensure high enantioselectivity over a broad range of substrates and to effect regioselective reactions, a hybrid donor atom approach was followed in the design of IndolPhos ligands **1**, possessing a phosphine and a

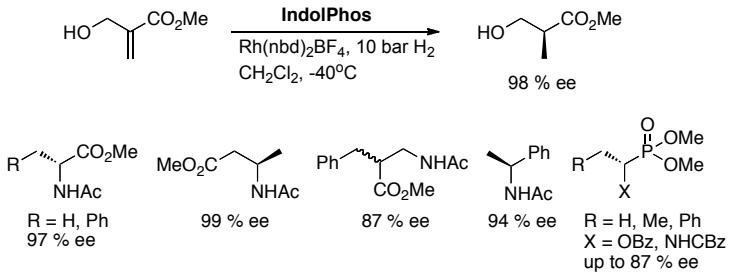
phosphoramidite group to bind to transition metals (Scheme 1). A small bite angle is desirable as this leads to strong chelation and hence tight metal binding, precluding the use of excess ligand. Importantly, the ligand must be synthesized in no more than two steps to be cheap and thus of industrial interest. Indole occurred to us as an ideal backbone of the hybrid bidentate ligand to meet the requirements outlined above. It allows for the synthesis in two steps to give IndolPhos **1**, which relies on a Bisnaphthol moiety as the privileged chiral element.

Scheme 1



In chapter 2 the synthesis, coordination chemistry and preliminary evaluation in the Rh-catalyzed asymmetric hydrogenation and hydroformylation by IndolPhos ligands are described. We developed a one-pot synthesis of the indolylphosphine intermediate by taking advantage of CO_2 as an *in situ* protecting and directing group for the selective lithiation on the 2-position of the indole. This affords these intermediates in good yields (up to 70 %) on a preparative scale (up to 15 g). Treatment with a strong base and the appropriate phosphorochloridite gave the desired hybrid ligand in excellent yields (up to 99 %). Application of ligands **1** in the asymmetric hydrogenation of benchmark substrates methyl 2-acetamidoacrylate and dimethyl itaconate gave the enantiomerically enriched products quantitatively in up to 98 % ee.

Scheme 2



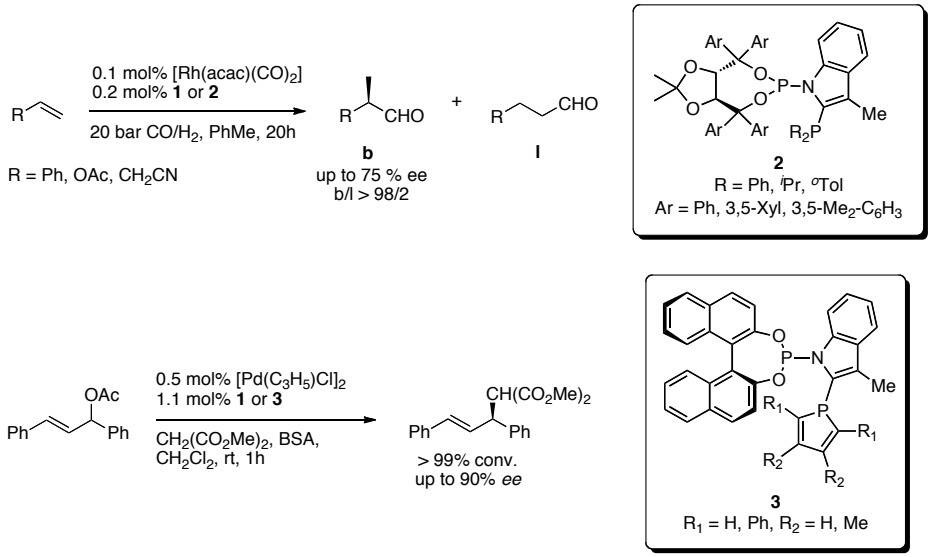
In chapter 3 and 4 we studied the scope of the IndolPhos-Rh catalyzed asymmetric hydrogenation towards the synthesis of relevant chiral targets such as the Roche ester, α- and β-amino acids, and amino- and hydroxyphosphonates (Scheme 2). These

molecules find their application in natural product synthesis and active pharmaceutical ingredients. Furthermore, the broad substrate scope showcases the generality of these catalysts, making them suitable candidates for industrial hydrogenations.

The kinetics and mechanism of the asymmetric hydrogenation using IndolPhos ligands was studies in detail in chapter 5. The catalysts appear to be highly active giving turnover frequencies up to 90 000 h^{-1} and turnover numbers up to 30 000, thereby satisfying the criteria for industrial application. Moreover, using DFT calculations it was found that the catalysts selectively bind to one prochiral face of the substrate, which gives rise to a lock-and-key mechanism of enantioselection. The latter is unusual as for many other systems an anti-lock-and-key mechanism was found. It seems to be the result of the hybrid donor atom approach as such a mechanism was found previously for P,S ligands.

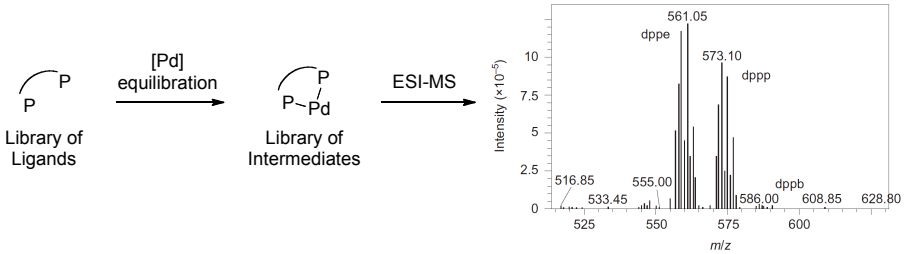
The use of IndolPhos ligands **1** in other relevant asymmetric transformations for the synthesis of active pharmaceutical ingredients and intermediates is described in chapters 6 and 7. In chapter 6 ligands **1** and their Taddol derivatives **2** are successfully applied in the asymmetric hydroformylation of several alkenes (Scheme 3, top), giving rise to good enantioselectivities (up to 75 % ee) and high b/l ratio's (> 98/2). Surprisingly, when examining differently substituted Taddol derived ligands **2** in the hydroformylation of vinyl acetate (R = OAc), a switch of enantioselectivity was observed. Mechanistic investigations suggest that this is the result of a different conformation of the active species depending on the ligand's substituents, which lead to opposite absolute configurations of the product.

Scheme 3



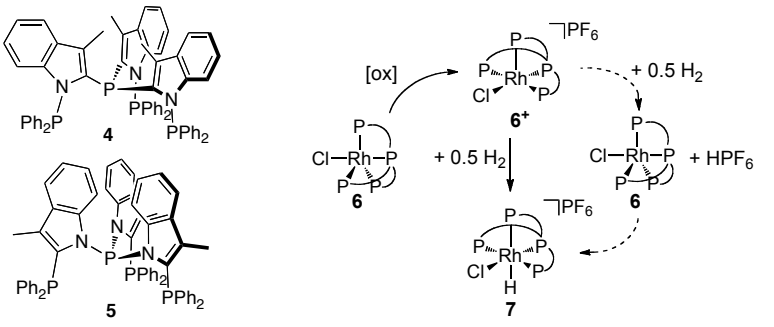
In chapter 7 we evaluated ligands **1** and IndolPhosphole ligands **3** in the Pd-catalyzed asymmetric allylic alkylation. They give highly active catalysts, which yield the alkylation products in high enantioselectivities of up to 90 % ee (Scheme 3, bottom). The Pd-allyl intermediates were studied in detail by X-ray crystallography and 2D NMR spectroscopy that allowed us to propose a rationale for the observed mode of enantioselection. The hybrid character of the ligand directs the regioselective attack of the nucleophile on the Pd-allyl intermediate. In addition to disubstituted allylic substrates, also mono-substituted substrates were converted in high enantioselectivity (up to 81 % ee).

Scheme 4



Chapter 8 deals with the development of a novel catalyst selection tool, based on intermediate stability measured by mass spectrometry. A library of ligands is equilibrated with a metal precursor to form a dynamic mixture of catalytic intermediates, which are quantified by electrospray ionization mass spectrometry (ESI-MS, Scheme 4). The more abundant species will be the most stable and less stable species will be present in smaller amounts. The stability of the intermediates relates inversely with the reactivity in the catalytic reaction, and hence the less-abundant species represent the most-active catalysts, 'the survival of the weakest'. We demonstrated this concept in the Pd-catalyzed allylic alkylation reaction using simple diphosphine and IndolPhos ligands (**1**) and supported our results with high-level DFT calculations. An almost quantitative correlation was found between intermediate

Scheme 5



stability and catalyst activity, confirming our hypothesis and validating the selection method.

The modular synthetic sequence to prepare IndolPhos ligands was used in chapter 9 to create C_3 symmetric tripodal tetraphosphine ligands **4** and **5** (Scheme 5). The strong electron-donating properties in conjunction with their ability to fully embrace and thus protect coordinated metal ions such as Rh (**6**), resulted in the formation of highly stable Rh^{II} metalloradicals (**6**$^+$), which are otherwise very reactive and unstable. However, these radicals maintain their ability to activate small molecules, as was demonstrated in the activation of dihydrogen to form the corresponding Rh^{III} hydride (**7**). Such activation can serve as a starting point for hydrogen atom transfer catalysis.

In conclusion, the approaches in catalyst design and selection presented in this thesis can make a valuable contribution towards more sustainable chemical processes and a more efficient use of scarce and valuable resources. The high activity and enantioselectivities provided by catalysts based on IndolPhos in a number of asymmetric transformations and for a broad range of substrates make these systems good candidates for the use as ligands in industrial applications. The novel selection method, 'survival of the weakest', is still in an early stage of its development but may be implemented in the future to find the optimal catalyst more rapidly. This would preclude time-consuming and waste-generating catalyst testing, which results in a more efficient and sustainable catalyst development process.