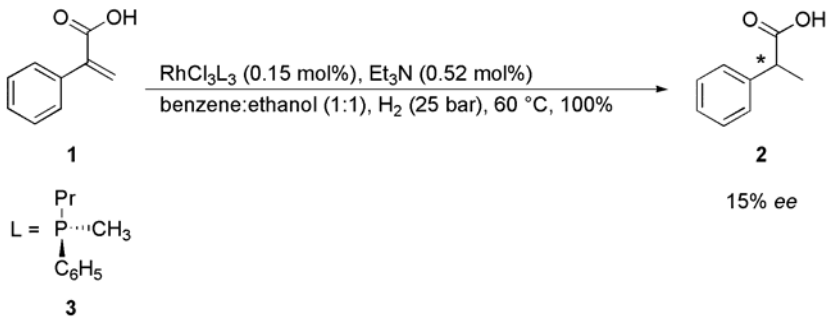
1 Introduction

1.1 Asymmetric Catalysis Breakthrough

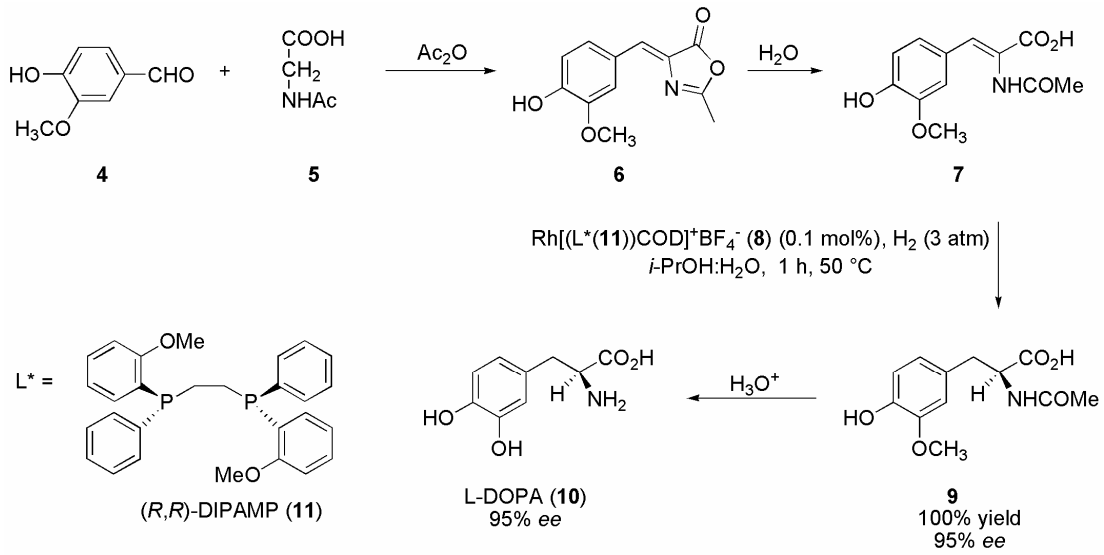
In 1848, Pasteur introduced the revolutionary concept of "dissymmetry" after he carried out the first enzymatic kinetic resolution. Starting from racemic ammonium tartrate, the organism *Penicillium glauca* selectively metabolized (*d*)-ammonium tartrate.[1] Since then, a wide variety of different routes have been developed to access enantiomerically pure compounds; chiral pool strategy, asymmetric synthesis based on chiral auxiliaries, enantioselective reactions by means of chiral reagents, chiral synthetic catalysts or enzymes. In 1968 Knowles, inspired by Horner's syntheses of chiral phosphines, was at the origin of the major breakthrough in asymmetric catalysis.[2] He showed that it was possible to induce enantioselectivity with a synthetic asymmetric rhodium complex derived from Wilkinson's catalyst.[3] The hydrogenation of styrene derivatives such as α-phenylacrylic acid (**1**) gave the optically active hydratropic acid (**2**) with an enantiomeric excess of 15% using an enantiopure methylpropylphenylphosphine ligand (**3**) (Scheme 1).



Scheme 1.

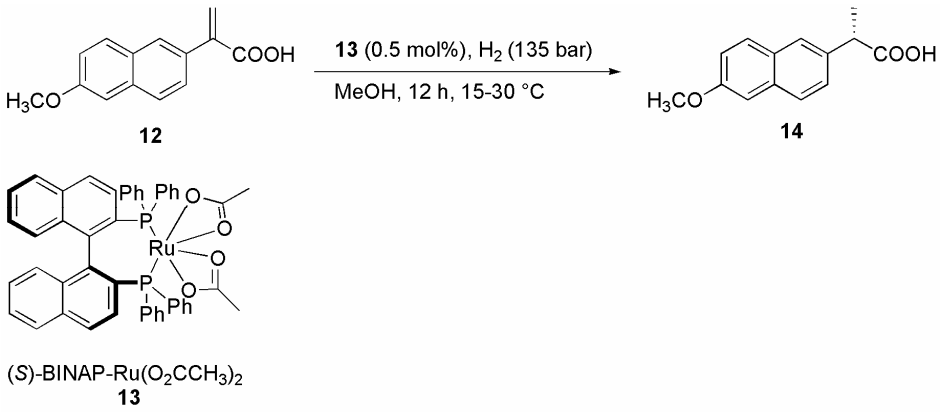
1.2 Industrial Applications of Chiral Transition-Metal Complexes

Knowles and co-workers later developed a chiral diphosphine-rhodium complex **8** that gave much higher *ee* and that catalyzed the hydrogenation of enamide **7** to a precursor of L-DOPA (**9**), used in the treatment of Parkinson's disease. This led to the first commercial use of a chiral transition-metal complex (Scheme 2).[4]



Scheme 2.

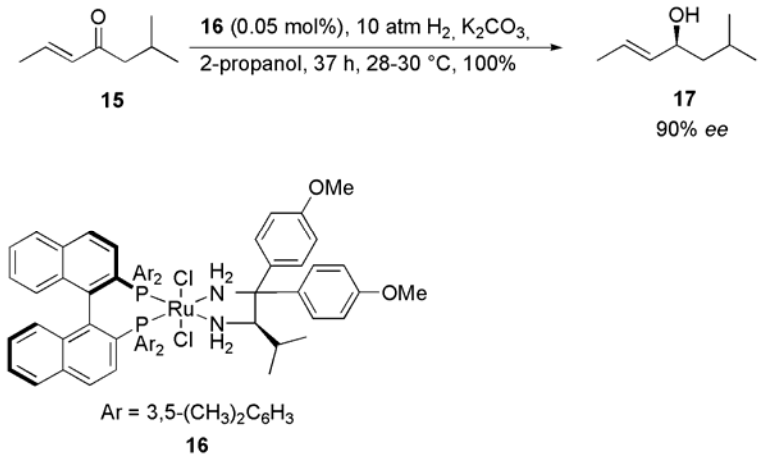
The expansion of asymmetric catalysis owes a great deal to Noyori's work. Nowadays, a number of transition-metal catalyzed reactions are highly enantioselective in the presence of diphosphine-binaphtyl ligand (BINAP) (**31b**).[5] In particular, BINAP-ruthenium(II) complexes catalyzed the hydrogenation of β,γ-unsaturated carboxylic acids[6], β-keto carboxylic esters[7] and functionalized ketones[8] to form highly enantioenriched products. For example, the BINAP-ruthenium(II) catalyst **13** was useful to catalyze the hydrogenation of the unsaturated carboxylic acid **12** to the anti-inflammatory agent naproxen[9] (**14**) in a yield of 92% and an enantiomeric excess of 97% (Scheme 3).



Scheme 3.

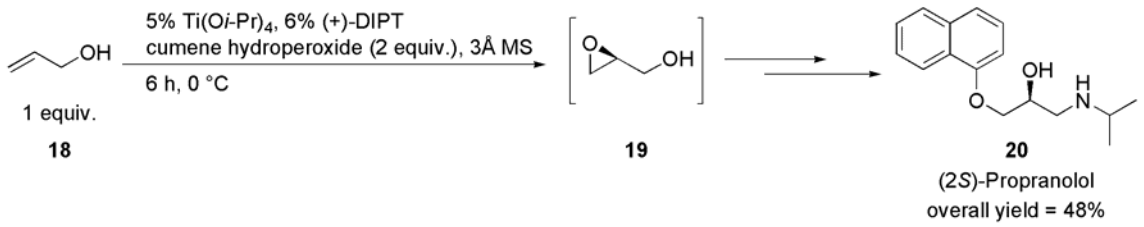
The research group of Noyori[10] demonstrated later that the *trans*-$RuCl_2$-(phosphine)$_2$(1,2-diamine) complex **16** preferentially hydrogenated the carbonyl group of an α,β-unsaturated

ketone instead of the double bond in a solution of 2-propanol in the presence of a weak base. This reaction was applied to the synthesis of compound **17**, a key building block for the preparation of the side chain of vitamin E (Scheme 4).



Scheme 4.

Parallel to the research on asymmetric hydrogenation, Sharpless's group developed transition-metal tartrate catalysts for the asymmetric epoxidation of allylic alcohols in 1980.[11] Later on, Sharpless and co-workers discovered that molecular sieves[12] could be used to further improve the efficiency of this asymmetric epoxidation. This process was applied on ton-scale in the industrial production of (*R*)- and (*S*)-glycidols, used to synthesize *β*-blockers based on (2*S*)-propranolol[13] (**20**) (Scheme 5). The alcohol **20** was synthesized in 5 steps from allylic alcohol **18** and was obtained in enantiomerically pure form after recrystallization in an overall yield of 48%.



Scheme 5.

More recently, Sharpless and co-workers devised a highly enantioselective osmium-catalyzed dihydroxylation of olefins.[14] They pre-mixed $K_2OsO_4.2H_2O$, a non volatile source of OsO_4,

$(DHQD)_2$-PHAL (**21**) or $(DHQ)_2$-PHAL (**22**), K_2CO_3 and $K_3Fe(CN)_6$ to form the active catalyst, which is easily prepared or commercially available (Figure 1).

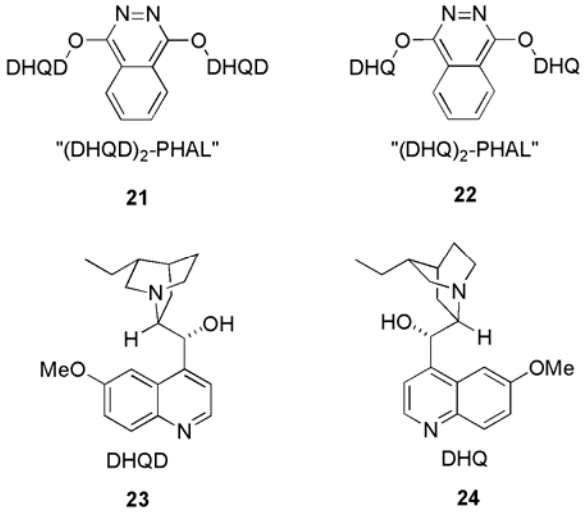
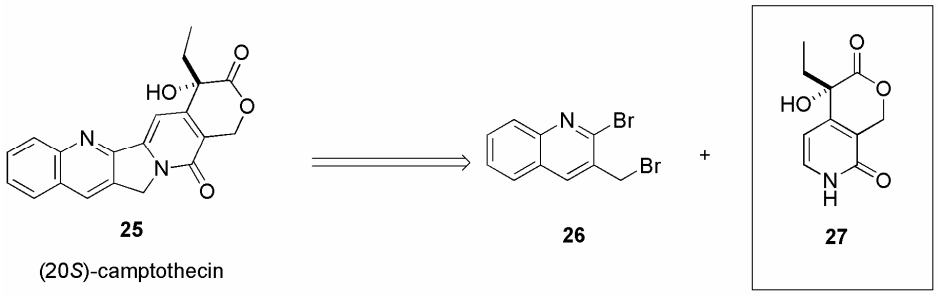


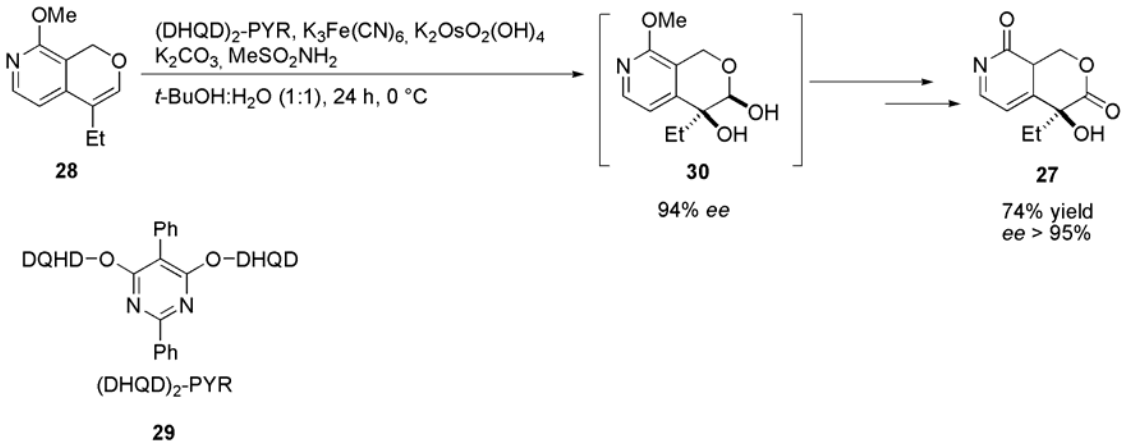
Figure 1.

An asymmetric dihydroxylation was used in the synthesis of (20*S*)-Camptothecin[13b] (**25**) which showed promising results in preclinical studies as an anticancer agent. Analogues of this alkaloid are now commercially available[15]. In 1992, Comins[16] proposed compound **27** as a key chiral intermediate (Scheme 6).



Scheme 6.

To prepare this intermediate Fang *et al.*[17] focused on the enol ether **28**, which was dihydroxylated under standard conditions using ligand $(DHQD)_2$-PYR (**29**) to give, after 2 additional steps, the corresponding pyridone **27** with an enantiomeric excess of >95% (Scheme 7).



Scheme 7.

Sharpless's epoxidation and dihydroxylation showed that synthetic catalysts could combine enzyme-like selectivity with sufficient generality for a wide range of substrates.

The successful work of Knowles, Noyori and Sharpless on asymmetric catalysis had obviously a great impact on academic research and the development of new drugs. All three were awarded with the Nobel Prize in chemistry in 2001.

1.3 Privileged Ligands in Asymmetric Catalysis

Enantiomerically pure compounds are in widespread use as pharmaceuticals, vitamins, agrochemicals, flavors and fragrances. Their synthesis using asymmetric catalysis requires a vast array of chiral ligands. Most of these are characterized by a "lock and key" specificity[18], which is also an enzyme feature. Therefore research scientists focused on the synthesis of chiral catalysts that would be selective for a broad range of reactions and substrates. Ligands of this kind are the so-called privileged ligands.[19] Important members include BINOL (**31a**), BINAP (**31b**), DuPhos (**32**), TADDOL (**33**), PHOX (**34**), BOX (**35a**), salen (**36**) and cinchona alkaloids (**37**) ligands (Figure 2).

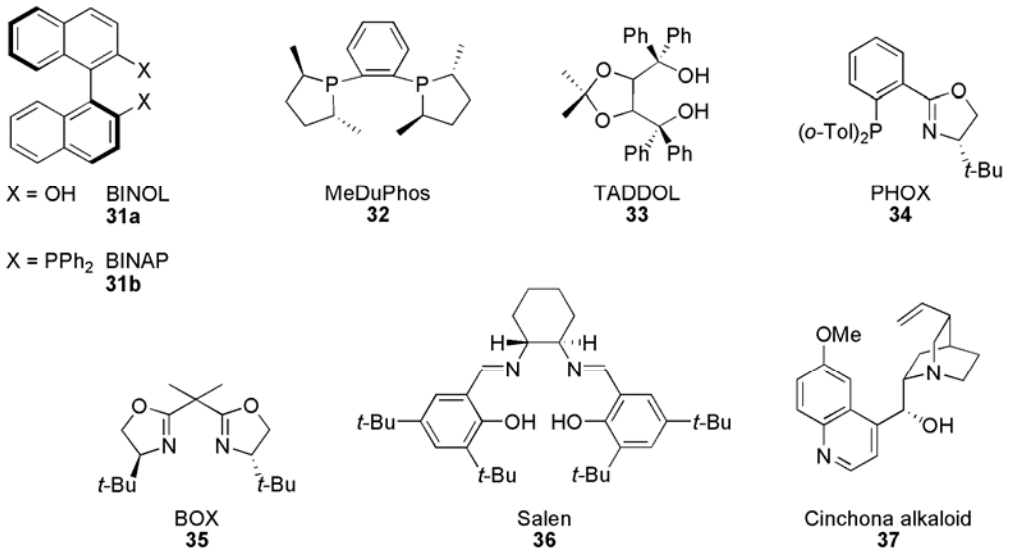


Figure 2.

One important characteristic of these ligands is the ease and flexibility of their synthesis. TADDOL **33** is derived from tartaric acid and is obtained in only two steps. Salen **36** and PHOX **34** ligands are synthesized from inexpensive chiral diamines and amino alcohols. Most of them possess C_2-symmetry which limits the number of possible catalyst-substrate arrangements and therefore reduces the number of competing reaction pathways. However, this feature does not necessarily imply that the ligand will be a privileged one. Ligands which are not C_2-symmetric can be highly efficient too; cinchona alkoloid derivatives[20] **37** for example are very selective for the aminohydroxylation of olefins,[21] heterogeneous hydrogenation of α-ketoesters[22] and phase transfer catalysis.[23]

The lack of common features for these ligands makes the identification of new privileged ligands problematic. High-throughput screening of catalyst libraries is still the most efficient way to discover new ligands.

1.4 Anionic and Neutral Ligands in Asymmetric Catalysis

Chiral ligands in asymmetric catalysis can be classified in two types: anionic and neutral ligands which form, in the presence of a metal, zwitterionic **38** and cationic complexes **39** (Figure 3).

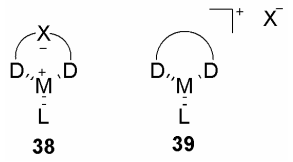


Figure 3.

The counterion of the cationic complex **39** is not necessarily a spectator. In many cases, it has an influence on the catalytic process.[24] First, the counterion competes with the substrate for coordination to the metal. Second, ion pairing may also influence stereochemistry.[24] For neutral ligands, the counterion is an additional variable to take into account for finding optimized reaction conditions. The zwitterionic complex **38** has obviously no counterion effect and this minimizes the number of parameters to screen.

1.5 Objectives of this Work

As one of the most versatile ligand structures, bis(oxazoline) ligands **35** have played a very important role in asymmetric catalysis over the last 25 years. To further develop its potential, a zwitterionic analogue, the borabox ligand **40**, was synthesized in the Pfaltz group.[25] The carbon bridging the two oxazoline units was replaced by a boron atom (Figure 4).

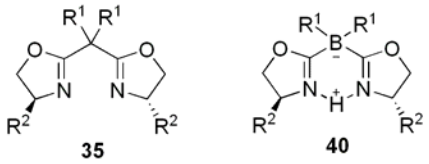


Figure 4.

The aim of this thesis was to demonstrate that the borabox ligands **40** were a valuable addition to the existing BOX ligands **35** with novel structural features.

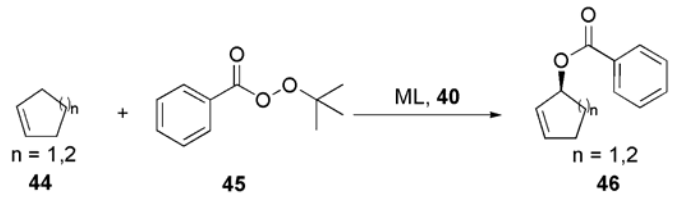
To obtain information about the characteristics of the borabox ligands **40** and its differences to the BOX ligands **35** crystallographic- and NMR-studies were performed.

This new ligand class was thought to show a similar versatility in asymmetric catalysis, but it was hoped to have a different or complementary behaviour compared to the BOX ligands due to the zwitterionic character of the corresponding metal complexes. Therefore several reactions were investigated in the presence of borabox ligands **40**.

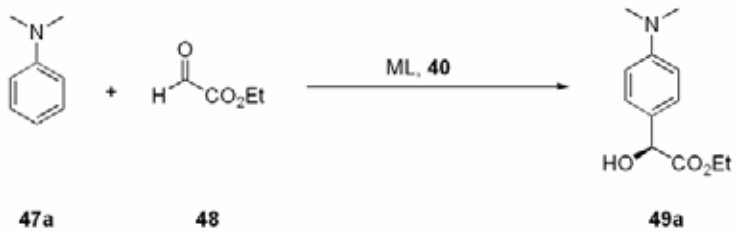
We studied first the Diels-Alder reaction, a benchmark reaction, and found suitable catalytic conditions (Scheme 8).

Scheme 8.

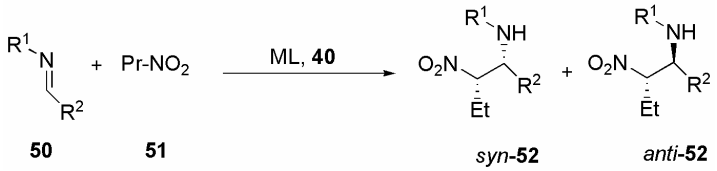
We became also interested in allylic oxidations, Friedel-Crafts and aza-Henry reactions (Schemes 9, 10 and 11), for which the reported enantioselectivities to date were still moderate.



Scheme 9.

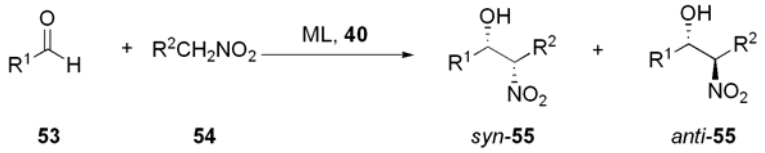


Scheme 10.



Scheme 11.

The Henry reaction was studied in greater detail (Scheme 12). After finding the optimal reaction conditions, the scope of the reaction was investigated.



Scheme 12.

Subsequently, C5,C5'-disubstituted borabox ligands (**56**) were synthesized (Figure 5). The objective was to improve the selectivity obtained in the Henry reaction by varying the substitution pattern of the ligand **56**.

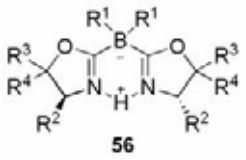


Figure 5.