Novel asymmetric copper-catalysed transformations
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Chapter 1

Introduction
1.1 Methodology development in organic chemistry
As a consequence of the increased complexity of target molecules in industry and academic research, the development of new methodology remains an important aspect of organic chemistry both in current time as well as for the future. Across the entire field of chemistry, from material science to pharmaceutical chemistry, efficient synthetic methods are crucial and of increasing importance, especially in the context of sustainable chemistry for the future.1-3

A key concept for methodology development in organic chemistry is synthetic efficiency, which was defined by Barry M. Trost as ‘the ability to convert readily available building blocks into the target molecule in relatively few synthetic operations that require minimal quantities of raw materials and produce minimal waste’.2 4 This concept of efficiency can be divided further into two major components: selectivity and atom economy. Selectivity can be categorized according to chemical reactivity (chemoselectivity), orientation (regioselectivity), and spatial arrangement (diastereo- and enantioselectivity). The development of novel methodology that is able to achieve both selectivity as well as atom economy must remain to be a prime goal in synthetic organic chemistry.1

1.2 Transition metal catalysis
Transition metal catalysis plays an important role in the continuing quest for novel reactivity.1,5 Besides opening up routes to novel products, transition metal catalysis also has the ability to solve the important issues of selectivity and atom economy in chemical reactions indicated in the first paragraph of this chapter. Due to the seemingly limitless combinations of transition metals and (chiral) ligands, transition metal catalysis can be utilized for a broad range of reactions including: hydrogenation,6-12 isomerization,13 oxidation,14-16 hydrosilylation17-20 and carbon-carbon bond forming reactions.1, 5, 21 Some selected pioneering examples are presented in Scheme 1.
Scheme 1  Selected examples of transition metal catalyzed transformations.

As a result of its wide applicability the field of transition metal catalysis has been recognized by the 2001 Nobel prize, for the development of ‘Chirally catalyzed hydrogenation and oxidation reactions’;\(^8\)\(^,\)\(^22\),\(^23\) the 2005 Nobel prize, for the development of ‘The metathesis method in organic synthesis’;\(^24\)\(^-\)\(^26\) and the 2010 Nobel prize, for the development of ‘Palladium-catalyzed cross couplings in organic synthesis’\(^27\),\(^28\).
1.3 Asymmetric C-C bond forming reactions

Carbon-carbon bond formation covers a wide spectrum of reactions and because the formation of new carbon-carbon bonds is arguably the most important process in organic synthesis its development and application is one of the most widely explored fields. A whole range of carbon-carbon bond forming reactions has been developed including: carbonylation, hydroformylation, hydrocyanation, (cross-)metathesis and a plethora of cross-coupling reactions (Suzuki, Negishi, Heck, Hiyama, and many more).

A fascinating aspect of many C-C bond forming reactions is the possibility to synthesize chiral molecules. Chirality and efforts towards the control of chirality have intrigued the chemical community since the introduction of the tetrahedral model of the carbon atom by Van ‘t Hoff and Le Bel 138 years ago. New standards and regulations in the chemical industry have led to an increasing demand for enantiopure molecules for the synthesis of pharmaceuticals, agrochemicals, flavors, fragrances and many other compounds. In response to this demand, the field of asymmetric carbon-carbon bond forming reactions grew explosively in the past few decades resulting in major breakthroughs. An important factor in the success of transition metal catalyzed asymmetric transformations has been the design of chiral ligands. By employing these chiral ligands, chemists are able to fine-tune the environment of the transition metal center, ideally leading to the desired reaction in high overall yield with exceptional levels of regio- and stereocontrol.

1.3.1 Asymmetric conjugate addition

One of the most versatile methods for enantioselective carbon-carbon bond formation is the asymmetric conjugate addition. This transformation is used as a key step in the synthesis of numerous natural products and biologically active compounds and has been the subject of intensive research over the past decades. In particular the copper-catalyzed asymmetric conjugate addition of organometallic reagents has proven to be successful in the synthesis of a wide range of enantiopure building blocks starting from a large variety of α,β-unsaturated substrates (see also Chapters 2, 3 and 4). In the asymmetric conjugate addition, the nucleophile is transferred to the β-position of α,β-unsaturated substrate. This process results in the formation of stabilized carbanion. Subsequent protonation leads to the isolation of the desired β-chiral product. Trapping with an electrophile leads to the formation of product bearing two stereocenters.
A major challenge in the asymmetric conjugate addition reaction is the control of the regioselectivity. Addition of a soft nucleophile generally takes place at the β-position of the unsaturated system, whereas 1,2-addition is favored in the case of hard nucleophiles like organometallic reagents. In the case of copper-catalyzed asymmetric conjugate addition reactions, careful tuning of the catalytic system can prevent the direct 1,2-addition of hard organometallic reagents to the electron withdrawing group and afford the desired β-chiral product with excellent enantiomeric excess.

An additional benefit of the copper-catalyzed asymmetric conjugate addition is the possibility for sequential transformations, i.e. trapping of the carbanion with an electrophile (Scheme 2), leading to the introduction of multiple stereocenters in a one-pot procedure with excellent enantio- and diastereoselectivity (see Chapter 4 for a more detailed discussion). The use of asymmetric tandem transformations is a very powerful approach in organic synthesis. Tandem transformations based on the asymmetric conjugate addition of organometallic reagents generally take advantage of the high enantioselectivities obtained in the conjugate addition reaction. The enolate formed in the asymmetric conjugate addition lends itself towards the development of sequential processes, in which trapping of the enolate leads to the formation of two or more stereocenters in a one-pot procedure (see Scheme 3).
In the past three decades considerable efforts have been directed towards the development of efficient catalytic systems and for this reason the copper-catalyzed asymmetric conjugate addition has been reviewed extensively.\textsuperscript{66, 73-77}

### 1.3.2 Asymmetric allylic substitution

Together with the asymmetric conjugate addition, asymmetric allylic alkylations are among the most powerful asymmetric carbon-carbon bond forming reactions known to date and have therefore received widespread attention over recent decades.\textsuperscript{75, 76, 85, 86} The asymmetric allylic substitution reaction provides access to optically active building blocks that are frequently employed in the synthesis of complex natural products and pharmaceuticals. During the past two decades significant progress was achieved in this field and numerous catalytic systems were developed suitable for a range of substrates bearing different leaving groups and with different organometallic based nucleophiles, \textit{i.e.} $R_2Zn$, $R_3Al$, $RMgX$, $RLi$ and $RBY_2$.\textsuperscript{75, 76}

![Scheme 4](image)

Scheme 4  Asymmetric allylic substitution. LG = leaving group.

The allylic substitution can proceed via two distinct pathways (Scheme 4). Depending on the catalytic system and the nucleophile, different ratios of $S_N2$ versus $S_N2'$ product are obtained. The palladium-catalyzed allylic substitution\textsuperscript{87-91} proceeds either via addition of a ‘soft’ nucleophile, such as malonates, directly to $\pi$-allyl intermediate $9a$ or, in the case of ‘hard’ nucleophiles, is proposed to proceed via a transmetallation to palladium to form $\pi$-allyl complex $9b$ followed by carbon-carbon bond formation. For the palladium-catalyzed allylic substitution different nucleophiles give a different ratio of $S_N2$ (10) versus $S_N2'$ (11) product. The copper-catalyzed version generally yields the chiral branched $S_N2'$ product 11 via transmetallation of the nucleophile to copper and formation of a $\sigma$-alkyl intermediate followed by reductive elimination.\textsuperscript{85} A more detailed overview of the copper-catalyzed allylic alkylation with organometallic reagents is presented in Chapter 5.
A significant advantage of both the copper-catalyzed asymmetric conjugate addition as well as the copper-catalyzed asymmetric allylic alkylation using organometallic reagents are the high compatibility with many functional groups, the low cost of the copper-salts used to form the active catalyst compared to e.g. palladium (Pd(OAc)$_2$: 10 g, €482 vs CuBr$_2$: 10 g, €40), and their excellent results with respect to regio- and enantioselectivity.

### 1.4 Aim and outline of this thesis

The aim of this thesis was to develop novel asymmetric copper-catalyzed transformations providing enantiopure building blocks. In Chapter 2, a highly efficient method for the asymmetric copper-catalyzed conjugate addition of Grignard reagents to $\alpha,\beta$-unsaturated 2-pyridylsulfones is described. Using a Cu/TolBinap complex, excellent enantioselectivities and high yields are obtained for a wide variety of aliphatic substrates. A complementary approach, the asymmetric copper-catalyzed conjugate addition of dialkylzinc reagents to $\alpha,\beta$-unsaturated 2-pyridylsulfones using a monodentate phosphoramidite ligand, is described in Chapter 3.

In Chapter 4, a sequential asymmetric copper-catalyzed conjugate addition/oxidative cyclization protocol is reported. This methodology allows for the synthesis of highly functionalized benzo[fused] spirocyclic compounds and a high degree of molecular complexity is achieved in a one-pot transformation.

Chapter 5 describes the development of a copper-based chiral catalytic system that allows carbon-carbon bond formation via allylic alkylation with organolithium reagents with extremely high enantioselectivities and is able to tolerate several functional groups. The most critical factors in achieving successful asymmetric catalysis with organolithium reagents were determined to be the solvent used and the structure of the active chiral catalyst. The active form of the catalyst was identified through spectroscopic studies as a diphosphine copper monoalkyl species.

Chapter 6 extends the utility of the use of organolithium reagents in asymmetric catalysis with the development of a highly efficient method for the asymmetric ring opening of oxabicyclic alkenes. Using a copper/chiral phosphoramidite complex together with a Lewis acid (BF$_3$•OEt$_2$), full selectivity for the anti isomer, high yields and excellent enantioselectivities were obtained for the multifunctional ring opened products.

The final chapter of this thesis, Chapter 7, describes the spectroscopic study of an asymmetric Mannich reaction, reported in 2007 by Mauksch and Tsogoeva, which was reported to be autocatalytic. The combined spectroscopic data indicate that this Mannich reaction is not catalyzed by the product. Several control experiments were performed, demonstrating that addition of the product does not accelerate product formation.
1.5 References

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