Copper-catalyzed enantioselective conjugate addition of Grignard reagent to non-activated acceptors
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Chapter 1: Introduction

This chapter introduces the importance and development of catalytic asymmetric conjugate addition of Grignard reagents to Michael acceptors. Addition of Grignards to different Michael acceptors has been enabled gradually and different catalytic systems were developed. Based on the progress reported in the existing catalytic systems, we have realized the addition to some more challenging Michael acceptors which have very low reactivity by combining highly reactive Lewis acids with Grignard reagents.
1.1 Catalytic enantioselective conjugate addition of organometallics

The past decades have seen a dramatic increase in the demand for enantiopure compounds for fine-chemicals and material science.\(^1\) Asymmetric conjugate addition (ACA) of organometallic reagents to Michael acceptors is a highly important and widely used method to construct carbon-carbon (C–C) bonds in an enantioselective manner.\(^2\)-\(^4\) Conjugate additions (1,4-additions) involve a reaction of nucleophiles (also referred to as donors) to alkenes or alkynes adjacent to an electron withdrawing group (also referred to as Michael acceptors). A broad spectrum of electron withdrawing groups in Michael acceptors are commonly used for such reactions, including aldehydes, ketones, esters, amides, nitriles, nitro, sulfonates, sulfoxides, phosphates, phosphonates etc.\(^5\) The common nucleophiles include organocuprates, organoboron reagents, organosilicon reagents, organozinc reagents, organoaluminium reagents, Grignard reagents and organolithium reagents. Among the numerous parameters that affect these often complex transformations are the nature of the metal ion, the catalyst structure (ligand and metal), solvent, aggregation, as well as competing catalytic species and pathways.\(^6\) Over the past years it has been demonstrated that transmetallation between organometallic reagents and several transition metals such as Ni,\(^7,8\) Cu,\(^9\)-\(^13\) Pd\(^14\) and Ti\(^15\)-\(^17\) can be used to generate a more reactive or softer organometallic reagent and this has proven to be crucial for efficient catalysis. Compared to other organometallics Grignard reagents are inexpensive, readily available and atom economic (when compared to aluminium and zinc reagents) organometallic reagents, offering a broader reaction scope than other organometallic reagents. However, the higher reactivity of Grignard reagents often leads to uncatalyzed 1,2- and 1,4-additions.\(^1\) This makes it difficult to promote the catalytic enantioselective pathway and outcompete the non-catalyzed racemic pathway. Thus, controlling both the regio- and enantioselectivity of reactions with Grignards reagents is often very challenging. But owing to continuous effort, considerable progress has been made over the last decade in catalytic asymmetric conjugate addition of Grignard reagents to Michael acceptors, and discussion of these advances will make up a large part of this chapter.

1.2 Catalytic asymmetric conjugate addition of Grignards to \(\alpha,\beta\)-unsaturated ketones

![Selected catalytic systems developed for the ACA of Grignard reagents to enones.](image)

**Figure 1:** selected catalytic systems developed for the ACA of Grignard reagents to enones.
During the last decades, α,β-unsaturated ketones have attracted much attention and are among the most investigated Michael acceptors. The first catalytic system for enantioselective conjugate addition of Grignards to α,β-unsaturated ketones was reported by Lippard et al. in 1988 using a catalytic amount of Cu-amide complex L1, resulting in up to 74% enantiomeric excess (ee) (Figure 1).\textsuperscript{18,19} Afterwards, a variety of catalytic systems were developed based on copper thiolates\textsuperscript{20-26} (L2-Cu–L5-Cu) and monophosphine ligands\textsuperscript{27-31} (L6–L8). However, these catalytic systems can only be applied to a limited substrate scope and most of them give less than 90% ee. Ligands L7 and L8 are the two exceptions in this list that can reach up to 92% enantioselectivity in some specific cases. Tomioka et al. developed a monophosphine ligand L7, derived from proline, for copper catalysis. When cyclohexenone was used as the substrate and n-HexMgCl as the nucleophile, the product was obtained with 90% yield and 92% ee but this requires 32 mol% of ligand L7.\textsuperscript{28} Another example is the chiral ferrocenyl monophosphine ligand L8 reported by Sammakia et al., which provided 82% yield and 92% ee when applied to copper-catalyzed asymmetric conjugate addition of n-BuMgCl to cycloheptenone.\textsuperscript{31}

\begin{center}
\textbf{Scheme 1:} ferrocenyl-based diphosphine ligands for the copper-catalyzed ACA of Grignard reagents to cyclic enones.
\end{center}

A breakthrough was made by Feringa and coworkers in 2004 when they introduced the commercially available ferrocenyl-based diphosphine ligands for copper-catalyzed asymmetric conjugate additions of Grignard reagents to cyclic enones, resulting in up to 96% enantioselectivity (Scheme 1).\textsuperscript{32} First ligands L9–L15 were screened with EtMgBr as the nucleophile and cyclohexenone 1b as the Michael acceptor. Ligands L9, L11 and L12 all worked well in this reaction, providing enantioselectivities higher than 90%. Screening of the scope of Grignard reagents with TaniaPhos ligand L9 resulted in products with good yields and enantioselectivities higher than 90% ee when using linear aliphatic Grignards, including MeMgBr. In contrast, the α- and β-branched aliphatic Grignards resulted in poor enantioselectivities. However, when JosiPhos ligand L13 was used in combination with copper salt, 54% and 92% ee was obtained with i-PrMgBr and i-BuMgBr respectively, a much better result than that obtained with TaniaPhos L9 as a ligand. Finally, this catalytic system can be extended to cyclopentenone 1a, cycloheptenone 1c and even the α,β-unsaturated lactone 1d, in all cases providing moderate to high enantioselectivities.
Scheme 2: copper-catalyzed ACA of Grignard reagents to $\beta$-methyl cyclohexenone with ligand L16.

Scheme 3: copper-catalyzed ACA of Grignard reagents to cyclic enones with ligand L17.

Following the report of Feringa et al., much effort has gone into the asymmetric conjugate addition of Grignard reagents to cyclic enones, and several new catalytic systems were developed. Alexakis et al. reported the copper-catalyzed enantioselective addition of Grignard reagents to $\beta$-methyl cyclohexenone 3a with N-heterocyclic carbene ligand L16, realizing the construction of challenging all-carbon quaternary chiral centers (Scheme 2), while the best results (96% ee) were obtained with $i$-BuMgBr. Other Grignard reagents including linear Grignards (EtMgBr and n-BuMgBr) and bulky Grignards ($i$-PrMgBr, c-PentMgBr, c-HexMgBr, PhMgBr) led to only moderate ee (66%–85%). Alexakis and co-workers also reported the application of a series of monophosphine ligands (SimplePhos ligands) for the addition to cyclic enones (Scheme 3). The best results (86% ee) were obtained with Ligand L17 when it was applied to copper-catalyzed asymmetric conjugate addition of $n$-OctMgBr to cyclohexenone 1b. However, the drawback of this catalytic system is that the results with bulky Grignards and other cyclic enones are worse.

Scheme 4: copper-catalyzed ACA of Grignard reagents to $\beta$-alkyl substituted cyclohexenones with ligand L18.

Figure 2: products obtained from the ACA of Grignard reagents to cyclohexenone with ligand L19 or L20.
In 2008, Tomioka et al. reported the Cu-catalyzed asymmetric addition of several Grignard reagents to β-alkyl substituted cyclohexenone 3 with another type of \( N \)-heterocyclic carbene ligand \( \text{L18} \), and the ees of the products were up to 80% (Scheme 4).\(^{35} \) In the same year, Schmalz et al. reported the use of TADDOL derivatives \( \text{L19} \) and \( \text{L20} \) as the chiral ligands in combination with CuBr·SMe\(_2\) (Figure 2). The products 2a–2e obtained from the addition of different Grignard reagents, including bulky Grignards to cyclohexenone 1b were obtained with good ee (82%–92%), but lower yields (49%–88%). Ligand \( \text{L19} \) is more suitable for linear Grignards while \( \text{L20} \) is more suitable for bulky Grignards.\(^{36} \)

Scheme 5: copper-catalyzed ACA of Grignard reagents to β,δ,δ-trisubstituted cyclohexenones with ligand \( \text{L21} \).

Based on the existing \( N \)-heterocyclic carbene ligands, Alexakis et al. developed a series of new \( N \)-heterocyclic carbene ligands in 2010 from which only ligand \( \text{L21} \) has a better catalytic effect (Scheme 5).\(^{37} \) When less sterically hindered Grignard reagents were added to β,δ,δ-trisubstituted cyclic enones 5, the ee is increased to 73%. In contrast, MeMgBr and bulky Grignards gave very low enantioselectivities. Later, they reported the enantioselective 1,4-addition of Grignard reagents to β-alkynyl substituted cyclohexenones 7 with \( N \)-heterocyclic carbene ligands (Scheme 6).\(^{38} \) They found that ligand \( \text{L22} \) has
excellent catalytic ability for a broad substrate scope, and the 1,4-addition products 8a−8m can be obtained with yields up to 98% and enantioselectivities up to 96%. In 2012, the same authors synthesized the second generation N-heterocyclic carbene ligands, and found that their catalytic performance is generally better than that of the first generation. The influence of the structure of the ligands on their catalytic performance is summarized in Figure 3.39

Figure 3: summary of the required structural components of N-heterocyclic carbene ligands.

![Figure 3](image)

Scheme 7: ACA of n-BuMgCl to cycloheptenone catalyzed by L23-Cu.

![Scheme 7](image)

Figure 4: TARTROL derivatives developed for the copper-catalyzed ACA of Grignards to cyclohexenone.

Also in 2012, a variety of TADDOL derived thiolato-Cu complexes was prepared by Seebach et. al. and applied in the enantioselective conjugate addition of Grignard reagents.40 The best results were obtained in the addition of n-BuMgCl to cycloheptenone 1c (Scheme 7). Using only 0.5 mol% of the air stable tetramer copper catalyst L23-Cu in THF it was possible to obtain 84% ee and more than 95% conversion of 1c. In 2013, Schmalz et. al. reported a series of TARTROL derivatives as the chiral ligands for copper-catalyzed ACA of Grignards to cyclohexenone 1b (Figure 4).41 Among these ligands, ligand L24 has the best performance, leading to enantioselectivities of up to 84%.

α-Substituted unsaturated cyclic enones are more challenging substrates for asymmetric conjugate additions due to their lower reactivity. Furthermore, two chiral centers will be generated at both the α and β positions after addition, thus a good catalyst must give not only a good enantioselectivity but also a good diastereoselectivity. In 2014, Alexakis et. al. first reported the Cu-catalyzed asymmetric conjugate addition of Grignard reagents to α-substituted cyclic enones, using the second generation N-heterocyclic carbene ligand L30.42 They found that addition of i-PrMgBr to α-methyl cyclopentenone and α-methyl cyclohexenone affords the highest enantioselectivities, with ers of 92:8 and 90:10, respectively. In contrast, the diastereoselectivities are moderate. However, when the intermediate magnesium enolate 10 was trapped with electrophiles like benzyl bromide
and allyl bromide, the diastereoselectivities become excellent (Scheme 8, 11a–11l). In the same year, Minnaard et. al. also reported the ACA of Grignards to α-methyl cyclic enones catalyzed by the copper complexes of ferrocenyl-based diphosphine ligands and phosphoramidite ligands.43 Rev-JosiPhos Ligand L31 was the best performing ligand in this case. The results were similar to those obtained in the work of Alexakis et. al. when addition was performed with linear Grignards, whereas addition with bulky Grignards led to worse results. Similarly, trapping with electrophiles provided a variety of products with high drs (Scheme 9).

\[
\begin{align*}
\text{O} & \quad + \quad \text{i-PrMgBr} \\
& \quad \xrightarrow{\text{L30 (1 mol%), Cu(Otbf)₂ (0.75 mol%)}} \quad \text{Et₂O, -30 °C} \\
& \quad \xrightarrow{\text{OMgBr}} \quad \text{HMPA eletrophile} \\
& \quad \xrightarrow{-30 °C to RT, 12 h} \quad \text{dr} \\
& \quad \xrightarrow{\text{L30}} \quad \text{HO} \\
\end{align*}
\]

\[
\begin{align*}
\text{11a, 85% yield} & \quad 92.8 \% \text{ er}, 99.1 \text{ dr} \\
\text{11b, 71% yield} & \quad 92.8 \% \text{ er}, 83.17 \text{ dr} \\
\text{11c, 47% yield} & \quad 92.8 \% \text{ er}, 99.1 \text{ dr} \\
\text{11d, 52% yield} & \quad 92.8 \% \text{ er}, 99.2 \text{ dr} \\
\text{11e, 45% yield} & \quad 92.8 \% \text{ er}, 99.1 \text{ dr} \\
\text{11f, 64% yield} & \quad 92.8 \% \text{ er}, 87.13 \text{ dr} \\
\text{11g, 49% yield} & \quad 90.10 \% \text{ er}, 99.1 \text{ dr} \\
\text{11h, 62% yield} & \quad 90.10 \% \text{ er}, 99.1 \text{ dr} \\
\text{11i, 51% yield} & \quad 90.10 \% \text{ er}, 99.11 \text{ dr} \\
\text{11j, 78% yield} & \quad 90.10 \% \text{ er}, 99.1 \text{ dr} \\
\text{11k, 50% yield} & \quad 90.10 \% \text{ er}, 99.1 \text{ dr} \\
\text{11l, 49% yield} & \quad 90.10 \% \text{ er}, 99.1 \text{ dr} \\
\end{align*}
\]

Scheme 8: products obtained from the copper-catalyzed ACA of i-PrMgBr to α-methyl cyclic enones with ligand L30 and the following trapping with electrophiles.

\[
\begin{align*}
\text{O} & \quad + \quad \text{n-PentMgBr} \\
& \quad \xrightarrow{\text{L31 (6 mol%), CuBr-SCN (6 mol%)}} \quad \text{DMF, -78 °C} \\
& \quad \xrightarrow{\text{OMgBr}} \quad \text{DMF eletrophile} \\
& \quad \xrightarrow{-78 °C to RT, 20 h} \quad \text{dr} \\
& \quad \xrightarrow{\text{L31}} \quad \text{HO} \\
\end{align*}
\]

\[
\begin{align*}
\text{11m, 67% yield} & \quad 91.9 \% \text{ er} \\
\text{11n, 75% yield} & \quad 91.9 \% \text{ er}, 82.18 \text{ dr} \\
\text{11o, 60% yield} & \quad 91.9 \% \text{ er}, 82.18 \text{ dr} \\
\text{11p, 90% yield} & \quad 91.9 \% \text{ er}, 90.10 \text{ dr} \\
\text{11q, 70% yield} & \quad 91.9 \% \text{ er}, 80.20 \text{ dr} \\
\end{align*}
\]

Scheme 9: products obtained from the copper-catalyzed ACA of n-PentMgBr to α-methyl cyclopentenone with ligand L31 and the following trapping with electrophiles.

Apart from the common cyclic enones, there are also some reports on chromones. Employing the copper complex of the same ligand L31, Feringa et. al. successfully realized the enantioselective 1,4-addition of Grignards to chromones.44 Different Grignards including the bulky Grignards as well as a variety of substrates with substituents on the phenyl ring are tolerated, giving excellent yields and ee (Scheme 10).
Scheme 10: products obtained from Cu-catalyzed ACA of Grignard reagents to chromones with ligand L31.
Scheme 11: products obtained from copper-catalyzed ACA of Grignard reagents to acyclic enones with ligand L14.

Most cyclic enones are locked into the s-trans conformation, whereas acyclic enones are in s-cis/s-trans conformational equilibrium. Therefore, asymmetric conjugate additions of Grignards to acyclic enones are more challenging than additions to cyclic enones when it comes to asymmetric induction. However ferrocenyI-based diphosphine ligands were also successfully applied to acyclic enones, resulting in excellent regio- and enantioselectivities for a variety of substrates and Grignards (Scheme 11). In contrast to the cyclic enones, JosiPhos ligand L14 gave the best results for acyclic enones, providing 94% isolated yield and 90% ee for copper-catalyzed ACA of EtMgBr to (E)-3-nonen-2-one. Different substitutions of R1 are tolerated including linear and branched aliphatic chains and aromatic groups. However, the reactions only give excellent enantioselectivities when R2 is a linear chain, whereas moderate ee is obtained when R2 is bulky. Linear Grignard reagents are well tolerated, giving excellent enantioselectivities. But when bulky Grignards such as i-PrMrBr, i-BuMrBr and PhMgBr are used, the ee is merely moderate, ranging from 48% to 84%.

Figure 5: copper aminoarenethiolate catalysts and Phosphoramidites ligand L38.

Chiral copper aminoarenethiolates L2, L32-Cu−L35-Cu were also reported to be effective in the ACA of MeMgI to substrate 14w (Figure 5). However, the enantioselectivities of the reactions catalyzed by these complexes are moderate (50%−76%). Phosphoramidite ligand L38 was applied to the copper catalyzed ACA of Grignard reagents to acyclic enones 14 by Feringa et. al., but also in these reactionsthe enantioselectivities were moderate with a maximum ee of 80% (Figure 5).

In 2013, Zhang et. al. studied the ACA of Grignards to α,β,γ,δ-unsaturated linear enones with a series of phosphoramidite ligands and chiral metallocene-based phosphinooxazoline ligands. The reactions with ligand L8 gave the best results with 1,4-addtion products as the main products. Products 17a−17q were obtained with excellent regio- and enantioselectivities by methylation of a variety of substrates (Scheme 12). In contrast, other Grignards like EtMgBr or BnMgBr provided the products 17r and 17s with moderate or low ee.
Scheme 1: products obtained from Cu-catalyzed 1,4-addition of Grignard reagents to linear $\alpha$,$\beta$,$\gamma$,$\delta$-unsaturated linear enones with ligand L8.

1.3 Catalytic asymmetric conjugate addition of Grignard reagents to $\alpha$,$\beta$-unsaturated esters

Compared to $\alpha$,$\beta$-unsaturated ketones, there are fewer investigations into the ACA of Grignard reagents to $\alpha$,$\beta$-unsaturated esters. The lower intrinsic reactivity of $\alpha$,$\beta$-unsaturated esters relative to that of enones, and the challenge to control the different conformers present in acyclic unsaturated systems, may account for this paucity of versatile methodologies. In 2005, Feringa et al. first performed systematic studies on the enantioselective conjugate addition to $\alpha$,$\beta$-unsaturated acyclic esters with Grignards based on previous research related to ACA to $\alpha$,$\beta$-unsaturated ketones. Ligands L14 and L31 in combination with CuBr·SMe$_2$ exhibited excellent catalytic efficacy for addition of linear Grignards to a variety of substrates (Scheme 13). They found that ACA of less bulky Grignards to linear substrates catalyzed by Ligand L14 and CuBr·SMe$_2$ gave excellent yields and enantioselectivities. But for $\gamma$-branched substrates ligand L31 exhibited better catalytic efficiency than Ligand L14. Methylation was not successful with only 19% conversion obtained, although the ee was high at 93% (19q).
Scheme 13: products obtained from Cu-catalyzed ACA of Grignards to \( \alpha,\beta \)-unsaturated acyclic esters with ligands L14 and L31.
Scheme 14: products obtained from Cu-catalyzed ACA of Grignards to \(\alpha,\beta\)-unsaturated thioesters with ligand L14.

![Scheme 14](image)

Scheme 15: products obtained from Cu-catalyzed ACA of Grignards to \(\alpha,\beta\)-unsaturated acyclic esters with ligand L39.

![Scheme 15](image)

Scheme 16: methylation products of \(\alpha,\beta\)-unsaturated acyclic esters with ligand L39 at higher temperature.

The authors presumed that the low yield was caused by the low reactivity of MeMgBr, so they used more reactive \(\alpha,\beta\)-unsaturated thioesters to replace the \(\alpha,\beta\)-unsaturated esters for methylation.\(^{51}\) Using this strategy, ACA of linear Grignards including MeMgBr was very successful with ligand L14, leading to the formation of a variety of chiral \(\beta\)-substituted thioesters with excellent yields and ees (Scheme 14). However, addition of bulky Grignards such as \(i\)-PrMgBr and \(i\)-BuMgBr generated the thioesters 211 and 21m with very low
enantioselectivities. The application of this methodology in an iterative fashion has culminated in the construction of 1,3-oligomethyl (deoxypropionate) arrays used in the synthesis of mycocerosic acid and phthioceranic acid, both isolated from *Mycobacterium tuberculosis*. In 2007, Ji and Loh *et al.* reported that the complex of Tol-Binap L39 with Cul is also capable of catalysing enantioselective conjugate addition of Grignards to α,β-unsaturated esters. Moreover, a broader Grignard scope as well as more practical reaction temperatures of −40 °C are tolerated. Except for the linear Grignard reagents, bulky Grignards like i-PrMgBr and i-BuMgBr also give excellent yields and ee (Scheme 15). Even PhMgBr is tolerated, leading to the formation of product 23r with 80% yield and 74% ee. Addition of EtMgBr to different substrates including aliphatic and aromatic ones was successful, and excellent results were obtained. However, methylation gives a low yield (20%) in the same conditions because of the diminished reactivity of MeMgBr. Later, the authors found that raising the temperature from −40 °C to −20 °C allowed the yield to increase to 85%, while maintaining the 98% enantioselectivity. Using these new conditions, methylation of a variety of substrates succeeded with excellent performance (Scheme 16).

In view of the efficiency of this catalytic system, it was subsequently extended to different types of acyclic esters and thioesters by other research groups (Figure 6). Using Tol-Binap ligand L39, Minnaard and Feringa *et al.* successfully overcame the limitations of their previously reported ACA addition of Grignards to thioesters with JosiPhos ligand L14, namely: (1) the low reactivity towards addition of MeMgBr of aromatic substrates with substituents on the phenyl ring and (2) the poor enantioselectivity of the addition of sterically hindered Grignard reagents. In contrast, methylation of aromatic substrates 24 gave excellent enantioselectivities with ligand L39, although low conversions were observed for the substrates containing an electron donating group at the para-position. Addition of bulky Grignard reagents to substrates 25 also showed significant improvement of the ee compared with ligand L14. In 2010, Hall *et al.* applied this catalytic system to the 3-boronyl substituted α,β-unsaturated ester 26 and thioester 27. Excellent results were obtained for addition of both linear and bulky Grignards to substrate 26, except for MeMgBr and PhMgBr that led to low conversions. However, when the authors switched to substrate 27, both MeMgBr and PhMgBr gave excellent yields and ees. In 2014, Loh *et al.* applied this catalytic system to 3-silyl substituted α,β-unsaturated esters 28. Only additions with linear Grignards were reported, for which excellent results were obtained.

![Figure 6: different type of acyclic esters and thioesters that ligand L39 was successfully applied.](image-url)
Scheme 17: products obtained from Cu-catalyzed ACA of Grignard reagents to coumarins with ligand L31.

Research into ACA of Grignard reagents to α,β-unsaturated acyclic esters has made considerably more progress than for α,β-unsaturated cyclic esters, because the increased electron delocalization renders the latter less reactive. The pioneering work in this context was reported by Feringa et al. using TaniaPhos ligand L9 which was initially applied for the ACA of Grignards to cyclic enones and then extended to 5,6-dihydro-2H-pyran-2-one 1d (Scheme 1). Later, the same authors also reported the application of rev-JosiPhos ligand L31 to coumarins, in which case the ACA products using linear Grignard reagents were obtained with excellent results whereas addition of bulky i-PrMgBr gave only 63% ee (Scheme 17). Methyl or halogen substituents are well tolerated at either the 6- or 7-position, while disubstitution at the 6,7- or 5,7-positions resulted in decreased yields and enantioselectivities. When this catalytic system was extended to pyranone and 5,6-dihydro-2H-pyran-2-one, only addition with less bulky Grignard reagents was reported with good performance (Scheme 18). The only exception is the methylation of 5,6-dihydro-2H-pyran-2-one that gave only 50% ee.
Scheme 18: products obtained from Cu-catalyzed ACA of Grignard reagents to pyranone and 5,6-dihydro-2H-pyran-2-one with ligand L31.

1.4 Catalytic asymmetric conjugate addition of Grignards to other Michael acceptors

Scheme 19: products obtained from Cu-catalyzed ACA of Grignards to $\alpha,\beta$-unsaturated sulfones with ligand L39.

Chiral $\beta$-substituted sulfones are highly versatile intermediates because they can be easily transformed into chiral aldehydes, ketones, alkynes, alkenes, alkanes, and haloalkanes. Various organometallics have been employed to realize the enantioselective conjugate
addition to \( \alpha,\beta \)-unsaturated sulfones. An example with Grignards as nucleophiles was reported by Feringa et al.\textsuperscript{64} By using Tol-Binap ligand L39/CuCl as the catalyst and 2-pyridyl substituted sulfones 33 as the substrate, a variety of linear Grignards including MeMgBr was successfully added providing the corresponding addition products with high yields and \( ees \) (Scheme 19). Both linear and branched aliphatic substituents at the \( \gamma \)-position were well tolerated, whereas the phenyl substituent at the \( \gamma \)-position resulted in only 46\% \( ee \).

![Scheme 20](image)

Scheme 20: products obtained from Cu-catalyzed ACA of Grignard reagents to nitroolefins with ligand L31.

Finally, an example of Cu-catalyzed enantioselective conjugate addition of Grignards to nitroolefins was reported using rev-JosiPhos ligand L31.\textsuperscript{65} However, the very limited substrate scope was tested only with bulky Grignards \( t-BuMgCl \) or \( t-PentMgCl \), providing high enantioselectivities and moderate yields (Scheme 20).

1.5 Catalytic asymmetric conjugate addition of Grignards enabled by Lewis acid

Lewis acid (LA) activation of various reagents towards nucleophilic addition is a powerful tool that has become common practice in organic synthesis.\textsuperscript{66-68} In terms of Grignard reagents, there is a prerequisite for the application of LA to ACA, which is the compatibility of the LA with the Grignard reagents. In previous work from both our group as well as other groups, strong Lewis acids were found to be compatible with Grignard reagents, and have been successfully applied to a number of Michael acceptors to overcome their specific reactivity issues and enable successful ACA of Grignards. The most relevant two examples will be discussed below.

Conjugate addition of hard organometallics including Grignard reagents to \( \alpha,\beta \)-unsaturated aldehydes is highly challenging in terms of both regio- and enantioselectivity. Because of their high reactivity and the easy accessibility of the carbonyl moiety, the undesired 1,2-addition is very likely to occur, leading to an alcohol byproduct that results from 1,2-addition to the aldehyde. Addition of the 1,4-addition product enolate to an aldehyde moiety of the substrate (aldol reaction) produces another common byproduct. In 2010, Alexakis et al. reported the first regio- and enantioselective conjugate addition of Grignards to \( \alpha,\beta \)-unsaturated aldehydes using copper salt in combination with chiral ligand L39.\textsuperscript{69} However, the most important additive to ensure the success of the reaction is a
Lewis acid, or more precisely, a silylating reagent. The authors found that addition of TMSCl can significantly increase the regioselectivity of the reaction from 32% to 85% towards the formation of conjugate 1,4-addition product 38a with 90% ee, while the formation of aldol byproduct can also be suppressed (Scheme 21).69,70 Applying this catalytic system to different Grignards and substrates, resulted in moderate to excellent regio- and enantioselectivities.

**Scheme 21:** products obtained from Cu-catalyzed ACA of Grignards to α,β-unsaturated aldehydes with ligand L39 enabled by TMSCl.
Scheme 22: Lewis acid enabled ACA of Grignard reagents to alkenyl-heteroaranes with ligand L31.

Another highly important class of intermediates for natural products and pharmaceuticals synthesis are the chiral N-containing heterocyclic aromatic compounds. The catalytic asymmetric addition of organometallics to conjugated alkenyl-heteroaromatic compounds...
represents an attractive strategy to access valuable chiral heterocyclic aromatic compounds in enantiopure form. However, the intrinsically lower reactivity of these compounds stemming from the relatively weak activation of the heteroaromatic moiety limited the application of this strategy. Through the introduction of the strong Lewis acid BF$_3$·Et$_2$O into the Cu-based catalytic system, our group realized the first enantioselective conjugate addition of Grignards to alkenyl-heteroaranes with rev-JosiPhos ligand L31. The insensitivity to the presence of heteroatoms in the substrate, which could potentially interfere with the stability of the chiral copper catalyst, makes the reaction remarkably general (Scheme 22). Substrates with various different $N$-containing heteroaromatic groups, including thiazoles, oxazoles, pyrimidines, triazines and quinoline, are well tolerated and, give rise to a variety of chiral $\beta$-substituted heteroaromatic compounds. A variety of Grignards are also compatible with this catalytic system including linear and branched aliphatic Grignards as well as aromatic Grignards, leading to excellent results both in terms of enantioselectivity and product yields.

**Scheme 23:** Lewis acid enabled ACA of Grignard reagents to alkenylpyridines with ligand L31.
Later, the substrate scope was extended to both 2- and 4-alkenylpyridines using either BF$_3$·Et$_2$O or TMSOTf as the LA in combination with the same ligand L31. Various pyridine derivatives can undergo CA of a wide range of Grignard reagents, both linear and branched (Scheme 23). The catalytic system shows a remarkable functional group tolerance, providing a handle for further product transformations. The effect of different LAs on the reactions was also investigated. The results indicate that with weaker LAs (going from TMSOTf to TMSBr and TMSCl) the conversion decreases from 100% to 60%. In addition, when the LA becomes more bulky (going from TMSOTf to TESOTf, TBSOTf and to TBDPSOTf), the ee also decreases, from 93% to 62%. This demonstrates that both the electronic and the geometric properties of the LA significantly influence the reaction.

### 1.6 Outline of this thesis

As a result of decades of research, it is currently possible to perform catalytic asymmetric conjugate additions to many classes of Michael acceptors with excellent enantioselectivities and product yields. However, most of these examples comprise relatively reactive and conventional Michael acceptors. A straightforward comparison of the electrophilic reactivity of the conjugated double bond (Scheme 24) present in various α,β-unsaturated carbonyl compounds reveals a strong effect on their performance in conjugate addition reactions, with both very strong and very weak electrophiles performing less well. It is therefore not surprising that the main successes in conjugate additions were achieved with Michael acceptors in the middle range of the spectrum. On the other hand, conjugate additions to very reactive aldehydes were only partially tackled by the Alexakis group recently. Furthermore conjugate additions to far less reactive unactivated α,β-unsaturated carboxamides and carboxylic acids, which are of major importance in organic synthesis, are still unreachable despite decades of research in this direction. From previous reports on the LA promoted addition of Grignards to alkenyl-heteroaranes as well as on 1,2-additions to acylsilanes we have learned that highly reactive LAs can be compatible with Grignard reagents in specific reaction conditions, which allows quick conversion of substrates to their desired products before any reaction can occur between the Grignard reagents and the strong LAs. In these reactions, LAs play various roles, such as control of regioselectivity (1,4- and 1,2-addition), prevention of side reactions (reduction in case of acyl silanes) and substrate activation (alkenyl-heteroaranes). These results were prerequisite to the research carried out in this thesis. Gradually realizing that we might be able to realize more challenging transformations by combining reactive LAs and Grignard reagents, we were particularly interested in tackling the reactivity issues of amides and carboxylic acid Michael acceptors in ACA, but also in the use of less conventional substrates, such as quinolones as Michael acceptors in ACA reactions.

\[
R'\text{CHO} > R'\text{CH} = \text{O} > R'\text{CH} = \text{S} > R'\text{CH} = \text{O} > R'\text{CH} = \text{O} > R'\text{CH} = \text{O} \]

**Scheme 24:** reactivity sequence of different α,β-unsaturated carbonyl compounds.
Hence, chapter 2 describes the Cu-catalyzed enantioselective conjugate addition of Grignards to simple $\alpha,\beta$-unsaturated carboxamides enabled by using BF$_3$:Et$_2$O or TMSOTf as the LA to allow the unequalled chemo-reactivity and stereocontrol.

In chapter 3, mechanistic studies were performed which revealed the fate of the LA in each underlying step of the copper catalyzed conjugate addition of Grignard reagents to $\alpha,\beta$-unsaturated carboxamides, allowing us to identify the most likely catalytic cycle of the reaction.

Chapter 4 presents the first Cu-catalyzed direct asymmetric conjugate addition of alkyl Grignard reagents to $\alpha,\beta$-unsaturated carboxylic acids, enabled by forming a highly reactive intermediate in situ with LA.

Chapter 5 describes the first enantioselective 1,4-addition of Grignards to quinoline, enabled by LA and providing excellent 1,4/1,2-regioselectivity.
1.7 References