Catalytic enantioselective conjugate addition of organometallic reagents

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Document Version
Publisher's PDF, also known as Version of record

Publication date:
1996

Link to publication in University of Groningen/UMCG research database

Citation for published version (APA):

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Chapter 2

Carbon-Carbon Bond Formation by
Catalytic Enantioselective Conjugate Addition

2.1 Introduction

Conjugate addition reactions of carbon nucleophiles to α,β-unsaturated compounds are among the most widely used methods for carbon-carbon bond formation in organic synthesis. It is therefore not surprising that major efforts have been devoted to achieve asymmetric conjugate addition despite the often complicated nature of many 1,4-addition reactions. Addition of the nucleophile to the β-position of an electron-deficient alkene results in a stabilized carbanion. After protonation of the carbanion (E⁺ = H⁺) a β-substituted product is formed. Quenching of the stabilized carbanion with electrophiles provides α,β-disubstituted products with two newly created stereocenters (Eq. 2.1).

\[
\begin{align*}
R=\text{EWG} & \xrightarrow{\text{Nu}^-} R^-=\text{EWG} & \xrightarrow{E^+} R^=\text{EWG} \\
\text{EWG} & = \text{CHO, COR, CQR, CONR}_2, \text{CN, SO}_2\text{R, NO}_2, \text{etc.}
\end{align*}
\]

As carbon nucleophiles one can use a variety of organometallic reagents, "classical" Michael donors, carbanions derived from nitro alkanes, nitriles or dithianes, and enolates (and derivatives). Common substrates for conjugate addition reactions are α,β-unsaturated aldehydes, ketones, esters, amides, nitriles, sulfones, and nitro compounds. Typical problems associated with conjugate addition are regioselectivity and reversibility. Competition between 1,2- and 1,4-addition to enones is governed by several parameters, but in general the use of soft carbon nucleophiles results in high selectivities for conjugate addition products (1,4-addition, Eq. 2.2).

\[
\begin{align*}
\begin{array}{llllll}
\text{Nu}^- & \xrightarrow{\text{E}^+} & \text{Nu}^+ & \xrightarrow{\text{E}^+} & \text{Nu}^+ & \xrightarrow{\text{E}^+} \\
\text{O} & \leftarrow & \text{O} & \leftarrow & \text{O} & \leftarrow \\
\text{R} & \text{R'} & \text{R} & \text{R'} & \text{R} & \text{R'}
\end{array}
\end{align*}
\]

\[
\begin{align*}
\text{1,2-addition} & \quad \text{1,4-addition}
\end{align*}
\]
In Michael additions, which are often executed under thermodynamic controlled conditions employing stabilized carbanions, reversibility is not an uncommon feature (Eq. 2.3). The stereochemistry might be affected by such reversible processes, whereas the presence of a labile hydrogen at the α-carbon of the product (with respect to EWG) could be another complicating factor as racemisation or epimerisation can occur.

\[ X\rightarrow Y^- + R\rightarrow\text{EWG} \rightleftharpoons R\rightarrow Y^-\text{EWG} \quad (2.3) \]

The enormous utility of conjugate addition reactions in synthesis is partly a result of the large variety of donor and acceptor compounds that can be employed. Another important aspect is the high diastereoselectivity often observed. These features have been a strong impetus for the development of enantioselective conjugate additions. The use of natural product-based Michael type acceptors has been extremely successful, commonly leading to Michael products with high and predictable stereoselectivities.\(^{2,4,5}\)

Stoichiometric asymmetric conjugate additions have been developed along two lines: (1) using a chiral auxiliary-based Michael acceptor i.e. chiral α,β-unsaturated ester, amide, sulfoxide,\(^{2,5,6}\) or (2) by reaction of a chiral reagent with a prochiral electron-deficient alkene.\(^{2,3,6}\) In the latter case two strategies have been used mainly, namely chiral auxiliary based donors, such as enamines and enol derivatives, and chiral ligand modified organometallic reagents, in particular chiral cuprates, Grignard reagents, organozincates, and organolithium reagents. Natural product-based and synthetic organic ligands and auxiliaries have been successfully employed, but high diastereoselectivities were reached also with organometallic auxiliaries.\(^7\) Asymmetric conjugate addition reactions using stoichiometric chiral auxiliary-based Michael donors and acceptors and chiral organometallic reagents have been extensively covered by reviews and the reader is referred to these papers for specific examples.\(^{1-6}\)

It should be emphasised that several chiral auxiliary-based acyclic and cyclic α,β-unsaturated substrates, enolates, and enamines are now available which give enantioselectivities exceeding 95% in a variety of reactions. Furthermore, there are a number of organocopper reagents with chiral non-transferable ligands as well as organocuprates modified by additional chiral ligands known today, that provide 1,4-addition products with e.e. > 95%.

However, only for a limited number of prochiral acyclic and cyclic enones high enantioselectivities are reached (vide infra).\(^3\) Major improvements are necessary, in
Carbon-Carbon Bond Formation by Catalytic Enantioselective Conjugate Addition

particular with respect to the scope of chiral reagent-based methods. This becomes evident when one considers applications in practical synthesis of enantiomerically pure compounds employing conjugate addition as a key step. Even more challenging is the development of general methodology for enantioselective carbon-carbon bond formation using chiral non-racemic catalysts in combination with readily available organometallic reagents and Michael donors. A literature survey of this area is the subject of this Chapter with the emphasis on enantioselective conjugate addition catalysed by chiral transition metal complexes.

2.2 Asymmetric metal-mediated 1,4-addition

In order to achieve a rational synthesis of new chiral catalysts for enantioselective conjugate addition it is important to consider several factors that might govern the 1,4-addition step. Among these are: (1) the nature of organometallic reagent \( (R'')_nM \) (Eq. 2.4), (2) the ligands \( L_n \) associated with it, (3) the fact that most of these reagents are aggregated in solution (solvent dependent), and (4) the notion that stereoselectivity (as well as regioselectivity) can be affected by additional ligands, coordinating solvents and salts.

\[
(R'')_nML_n + \overset{\text{O}}{\underset{\text{R'}}{\text{R}}} \rightarrow \overset{\text{OML}_n}{\underset{\text{R'}}{\text{R}}} \quad (2.4)
\]

\[M = \text{Cu}, \text{Li}, \text{Zn}, \text{Mg}\]

Furthermore, activation of the electron deficient alkene by Lewis acid or cation complexation to the carbonyl moiety is often proposed as a means to tether the reagent, catalyst, and enone in order to increase stereoselectivity and enhance reactivity towards weaker nucleophiles. The coordinating metal can either be from the organometallic reagent, the catalyst, or additional metal ions (i.e. salts). The proposed intermediate \( I \) in the highly enantioselective (90% e.e.) conjugate addition of the (1R,2S)-ephedrine-based mixed cuprate, reported by Corey and co-workers,\(^8\) nicely illustrates additional lithium ion coordination between the oxygen of the enone and the cuprate ligand (Figure 2.1).
The use of Lewis acids, in particular Me₃SiCl or BF₃, often results in a dramatic increase of reaction rates in 1,4-addition reactions of cuprates, presumably by enone activation (Eq. 2.5a). Increased stereoselectivity, for instance, almost exclusive formation of IVa by Me₂CuLi addition to III in the presence of Me₃SiCl (Eq. 2.5b), and the formation of enol derivatives such as II, which can subsequently be used in electrophilic additions (tandem 1,4-addition-enolate processes), are additional important advantages.

\[
\begin{align*}
\text{LA} = \text{Me}_3\text{SiCl}, \text{BF}_3
\end{align*}
\]

Lewis acid catalysis has been extremely successful in 1,4-additions of enol silyl ethers (and tin-analogues). The role of the Lewis acid can be an activation of the enone and the silyl-enolate leading, via a cyclic transition state V (Figure 2.2), to Michael adducts with high stereoselectivities.
The high level of regulation in V that might be reached in these cases offers attractive possibilities for the development of new chiral Lewis acid catalysts for 1,4-addition. Moreover, stereoselectivity appears to be strongly Lewis acid- and substituent-dependent, as is illustrated in Eq. 2.6.\textsuperscript{12}

When enolate anions or other stabilized carbon nucleophiles are involved in conjugate addition reactions in the presence of chiral metal catalysts, the catalyst can exert its
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stereodirecting effect via formation of a chiral metalenolate VI (Figure 2.3) or by complexation and activation of the Michael donor VII (or both donor and acceptor). The geometry of the enolate (VIa or VIb) is a decisive factor in the π-face selectivity and syn-anti diastereoselectivity. Finally, it should be noted that the stereochemical result of 1,4-additions of enolate type carbon nucleophiles strongly depends on chelation or non-chelation control.

In Eq. 2.7a and Eq. 2.7b the open transition state model and the closed (chelated) transition state model for metalenolate additions to enones, leading to syn- and anti-adducts, respectively, are given for the case of a Z-enolate.

A number of highly diastereoselective conjugate additions of metalenolates has been developed, strongly stimulated by the results of stereoselective aldol reactions using well defined E- and Z-metalenolates and by exploring the coordination properties of several metals (in particular B, Li, Ti and Mg). Again enolate geometry, solvent, counterion, metal catalyst, and mode of addition can have a strong influence on the stereochemical result and all these variables need to be considered in designing an effective chiral catalyst for 1,4-addition.

The use of chiral metal catalysts for enantioselective carbon-carbon bond formation using organometallic reagents and other carbon nucleophiles will be described in the next sections. For the sake of completeness conjugate addition reactions using chiral crown ethers and bases are included.
2.3 Enantioselective conjugate addition of Grignard reagents

Chiral copper complexes as catalysts
Rapid progress has been made in recent years towards highly enantioselective conjugate addition reactions of chiral, ligand modified, cuprates and organocopper reagents with non-transferable ligands based on Grignard and organolithium compounds. It is surprising that despite many attempts, only very recently the first examples of successful 1,4-additions of Grignard reagents catalysed by chiral copper complexes were reported, albeit modest selectivities and limited scope were reached. Lippard and co-workers described the first catalytic conjugate addition of n-BuMgBr to 2-cyclohexen-1-one (2.2) (Eq. 2.8). Using a copper(I) complex derived in situ from chiral N,N'-dialkylaminotropone imine (H-(R)-CHIRAMT, 2.14, Figure 2.5), 3-butylenecyclohexanone was obtained in 14% e.e. The enantioselectivity of the reaction is significantly increased by the addition of hexamethylphosphoric triamide (HMPA) and silyl reagents (see Section 2.2).

Both HMPA and a bulky silyl reagent seem to be essential to reach high e.e.'s. The highest enantioselectivity (e.e. 74%, yield 53-57%) is obtained using 2 equivalents of t-butyldiphenyldimethylsilylchloride, 2 equivalents of HMPA and 4 mol% of chiral ligands 2.14 or 2.15. The role of HMPA and the silyl reagent remains rather obscure at present, but it seems that these additives suppress the uncatalysed conjugate addition. A slightly higher e.e. (78%) is obtained when a stoichiometric amount of copper and chiral ligand is used. Compared to n-BuMgCl poor enantioselectivities were found with MeMgCl or EtMgCl (30 and 14% e.e. respectively). Interestingly, the reaction with MeMgCl gave (R)-3-methylcyclohexanone in excess, instead of the S enantiomer obtained in the reaction with n-BuMgCl. This reversal indicates that the Grignard reagent is involved in the rate determining step of the reaction. Other enones are converted as well, though no enantioselectivity was observed. All these effects clearly demonstrate the complex nature of the catalytic sequence and in particular further study of additive effects will be necessary. Since the pioneering work of Lippard and co-workers several other groups have reported catalytic enantioselective conjugate additions of Grignard reagents.
reagents. The relevant results will be described in this section. The substrates and chiral catalysts are compiled in Figure 2.4 and 2.5, respectively.

\[
\begin{align*}
  &2.1 \ n = 0 ; X = CH_2 \\
  &2.2 \ n = 1 ; X = CH_2 \\
  &2.3 \ n = 2 ; X = CH_2 \\
  &2.4 \ n = 1 ; X = O \\
  &2.5 \ R, R' = Ph \\
  &2.6 \ R = Ph ; R' = Me \\
  &2.7 \ R = Me ; R' = Ph \\
  &2.8 \ R = Ph ; R' = CPh_3 \\
  &2.9 \ R = Ph ; R' = t-Bu \\
  &2.10 \ R = Ph ; R' = p-MeOPh \\
  &2.11 \ R = p-MeOPh ; R' = Ph \\
  &2.12 \ R = p-CIPh ; R' = Ph \\
  &2.13 \ R = Ph ; R' = p-CIPh
\end{align*}
\]

Figure 2.4 Substrates used in catalytic enantioselective conjugate addition reactions of Grignard and dialkylzinc reagents (see sections 2.3 and 2.5).

Van Koten and co-workers have reported the use of chiral copper(I) arenethiolate (2-[1-(R)-(dimethylamino)ethyl]phenylthiolate copper(I), (2.16)) as a catalyst for the enantioselective addition of MeMgI to benzylideneacetone (2.6) (Eq. 2.9).\(^\text{17}\) The enantioselectivity is highly dependent on the mode of addition. Only controlled, simultaneous addition of solutions of MeMgI and of 2.6 (at equal concentration) to catalyst 2.16 (9 mol\%) in diethyl ether afforded a relatively high enantioselectivity (76\% e.e.). This indicates that a cuprate reagent rather than free MeMgI is involved in the reaction.

\[
\begin{align*}
  \text{2.6 R' = Me ; X = H} \\
  \text{(R' = i-Pr, t-Bu ; X = Cl, Me, OMe)}
\end{align*}
\]

Using the optimal parameters found for MeMgI, the scope of this reaction has been examined for other Grignard reagents (n-BuMgI and i-PrMgI, 45 and 10\% e.e., respectively) and various acyclic enones (Eq. 2.9). Substrates with different para
substituents on the aromatic ring and steric bulk next of the carbonyl group gave products with slightly lower enantioselectivities (45-72% e.e.). However, the use of chalcone (2.5) (or cyclohexenone) furnished the 1,4-product with an e.e. of 0%.

Copper(I) thiolate complexes derived in situ from chiral mercaptophenyloxazolines 2.17-2.20, were reported by Zhou and Pfaltz to be effective in the 1,4-addition of n-BuMgCl to cyclic enones 2.1-2.3 (Eq. 2.10). Highest enantioselectivities were reached only when the Grignard reagent was added slowly at -78°C to the solution of enone, catalyst, and two equivalents of HMPA. The methyl and i-propyl derivatives 2.17 and 2.18 were found to be the most effective ligands, whereas the bulky derivative 2.19 gave markedly lower e.e.'s. Significant enantioselectivities were found only in the presence of HMPA. The use of trialkylchlorosilanes as additives (vide supra) resulted
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in substantial loss of selectivity. With ligand 2.18 the enantioselectivity of the 1,4-product increased with ring size of the cyclic enone (cyclopentenone, 16-37% e.e.; cyclohexenone, 60-72% e.e.; cycloheptenone, 83-87% e.e.). With respect to the Grignard reagent it was found that i-PrMgCl gave consistently higher e.e.'s than n-BuMgCl, whereas PhMgBr gave virtually racemic products. Despite the strong analogy between chiral catalysts 2.16 and the copper catalyst derived from ligands 2.17-2.20, only low enantioselectivities (e.e. < 20%) with acyclic enones were reported in the latter case.

A third catalytic system based on chiral copper(I) thiolate complexes was described by Spescha and Rihs. The chiral complex, prepared in situ from the lithium salt of 1,2,5,6-di-O-isopropylidene-3-thio-α-O-glucofuranose (2.21) and CuI, gave high yields and regioselectivities exceeding 98% in the addition of n-BuMgCl to enone 2.2. The enantioselectivity is strongly dependent on the reaction conditions and variation of a large number of reaction parameters resulted in e.e.'s up to 60%. The catalytic reaction was carried out by slow simultaneous addition of a solution of n-butylmagnesium halide and a solution of enone to a solution of the copper complex in order to avoid excess of reagents. A remarkable dependency on the halide in the Grignard reagent was observed and with PhMgBr only an e.e. of 20% was found. Reproducible results were found upon addition of a radical scavenger (2,2,6,6-tetramethylpiperidin-N-oxyl, TEMPO). Together with the dependency of the enantioselectivity on the turnover numbers, salts, and solvents these findings typically illustrate the complex nature of these catalytic systems.

Recently, Tomioka and Kanai reported the use of a chiral bidentate phosphine ligand in the copper catalysed addition of Grignard reagents to cyclic enones. The addition of several n-alkylmagnesium chlorides to enones 2.2 or 2.3 in the presence of 8 mol% of Cul and 32 mol% of 2.22 gave 1,4-products in good yields and with relatively high enantioselectivities (70-92% e.e., Eq. 2.11).
Grignard reagents, such as Me-, Ph-, and i-Pr-magnesium chloride and Grignard reagents prepared from the corresponding bromides or iodides, gave low e.e.'s and poor yields. Remarkably, the addition of n-butyl- or n-hexylmagnesium chloride to 5,6-dihydro-2H-pyran-2-one (2.4) was also effective, furnishing synthetically interesting chiral intermediates (90% e.e.).

Without doubt, the copper catalysts are highly promising in enantioselective conjugate additions of Grignard reagents and the first examples of e.e.'s exceeding 95% seem to be in close reach. One of the major problems to deal with, besides tuning of ligand and reaction conditions, are the different aggregates of the catalyst which are in equilibrium with each other, as they apparently are formed in the reaction medium. The aggregate formation probably depends on the concentration of reactants and additives, and results in different catalytically active species with different enantioselectivities.

Chiral zinc complexes as catalysts
The development of chiral zinc(II) complexes as catalyst for 1,4-addition reactions was based on the discovery of Isobe and co-workers of the facile conjugate addition of lithium triorganozincates. Subsequent studies resulted in selective alkyl group transfer from mixed trialkylzincates, the use of alkoxides as non-transferable ligands, and 1,4-additions of Grignard reagents mediated by N,N,N',N'-tetramethylenediaminezinc dichloride as reported by Jansen of our research group. Stimulated by these results stoichiometric and catalytic amounts of chiral diaminezinc complex 2.23 (Figure 2.5) were used in the 1,4-addition of i-PrMgBr to cyclohexenone (2.2). A catalytic amount (1 mol %) of 2.23 substantially increases yields, regioselectivities towards 1,4-adducts and enantioselectivities of the conjugate addition (21% e.e.). A number of chiral catalysts were prepared in situ from chiral ligands 2.24-2.28 and ZnCl₂ and screened in the model reaction (Eq. 2.12).

\[
\begin{align*}
&\text{2.2} \\
&\text{i-PrMgX} \\
&\text{ZnCl₂ (cat.)} \\
&\text{2.24-2.28 (cat.)} \\
&\text{THF, -90°C} \\
&\to \quad \text{(2.12)} \\
&\text{15-33% e.e.}
\end{align*}
\]

In all cases yields and regioselectivities are excellent and the highest enantioselectivity (33%) was found with 5 mol% of chiral ligand 2.28 and i-PrMgBr as Grignard reagent.
The enantioselectivity depends furthermore on a number of variables:

- With other alkyl- and aryl-Grignard reagents lower e.e.'s, as compared to i-PrMgX, were found.
- Both regio- and enantioselectivity improved by decreasing the temperature.
- The effect of chloride or bromide in RMgX on the enantioselectivity reverses with different chiral ligands. Similar effects have been observed in cuprate additions.
- A significant improvement of the enantioselectivity due to the presence of lithium ions was observed and the catalyst has preferentially to be prepared from the lithium salt of the ligand (for the lithium ion effect, see also Section 2.2).
- Higher enantioselectivities were attained by slow addition of i-PrMgX to a solution containing substrate and catalyst. It appears to be essential to keep a low concentration of organometallic species to prevent uncatalysed addition.

The modest enantioselectivities and the sensitivity to a large number of variables make it difficult to postulate a catalytic cycle. However, the enantioselective 1,4-addition can be rationalized by a model shown in Figure 2.6, given for the catalyst based on ligand 2.28.

![Proposed intermediate in the zinc catalysed conjugate addition of Grignard reagents to 2.2.](image)

Binding of the Grignard reagent via coordination of magnesium to the alkoxide exo to the bicyclic zinc complex can take place. Activation of the substrate, via coordination to zinc, involves a pentacoordinated zinc(II) intermediate, which brings Grignard reagent and enone in close proximity to allow alkyl transfer. In this stage a third metal (i.e. lithium) could be involved as proposed for cuprate additions (see also section 2.2). It should be noted that scrambling of both alkyl groups has been observed.

The zinc catalysed 1,4-addition of Grignard reagents is attractive as high yields and regioselectivities are found although it is obvious that the enantioselectivity needs
substantial improvement.

2.4 Catalytic enantioselective conjugate addition of organolithium reagents

The high reactivity commonly found for organolithium reagents compared to Grignard reagents and the preference for 1,2-addition make the development of an efficient catalyst for conjugate addition of RLi a particularly challenging goal. Significant enantioselectivities in catalytic alkyllithium additions have not been reported until Tanaka and co-workers recently realized the chiral alkoxyocuprate catalysed addition of MeLi to (E)-cyclopentadec-2-en-1-one (2.29) affording (R)-(−)-muscone with e.e. 99% (Eq. 2.13).

The chiral catalyst was prepared from amino alcohol ligand 2.30 by sequential addition of MeLi, CuI, and MeLi. The conditions for the catalyst preparation are very critical to reach high enantioselectivities. The use of 1 equivalent of THF, presumably as external ligand to the chiral cuprate, increases the e.e. significantly. Under optimised conditions, 36 mol% of chiral ligand 2.30 provides muscone virtually enantiomerically pure and in high yield. Despite impressive e.e.'s in this case further implementation awaits effective catalysis at lower catalyst concentration and high selectivities with other enones.

The enantioselective addition of phenyl- and 1-naphthyllithium to 1- and 2-naphthalene carboxylic esters of 2,6-di-t-butyl-4-methoxyphenol (BHA) catalysed by chiral diether 2.32 was reported by Tomioka and co-workers (Eq. 2.14).
This is an interesting case of ligand-accelerated organometallic carbon-carbon bond formation. The 1,4-addition in the absence of chiral ligand 2.32 was sluggish. Both 1- and 2-hydroxymethyl substituted dihydronaphthalene derivatives have been obtained via this catalytic process.

2.5 Conjugate addition of dialkylzinc reagents catalysed by chiral nickel complexes

Enantioselective carbon-carbon bond formation by 1,2-addition of organozinc reagents to aldehydes has become one of the most successful and active area’s of asymmetric synthesis in recent years. Although dialkylzinc reagents react extremely sluggish with carbonyl compounds, effective catalysis has been achieved by several ligands and transition metal complexes. The catalytic effect was explained by changes in geometry and bond energy of the zinc reagents. For example, dimethylzinc has a linear structure and is not reactive towards aldehydes or ketones (Figure 2.7). Upon coordination of triazine a tetrahedral configuration at the zinc atom and an elongated zinc-carbon bond is found, resulting in enhanced reactivity of the dialkylzinc reagent.

Figure 2.7 Structures of dimethylzinc (A) and its adduct with 1,3,5 -
Several catalytic 1,4-additions of diethylzinc to acyclic enones employing chiral nickel complexes have been developed. The substrates and chiral catalysts are compiled in Figure 2.4 and Figure 2.8, respectively. Based on work of Luche and Greene and co-workers, an enantioselective modification of the nickel catalysed alkyl transfer from diethylzinc to chalcone (2.5) was found by Soai and co-workers. The chiral catalyst, prepared in situ from NiBr₂ and (1S,2R)-N,N-di-n-butylnorephedrine (2.33), afforded (R)-1,3-diphenylpentan-1-one in 32% yield with 48% enantiomeric excess. Higher yields (>70%) were achieved with Ni(acac)₂ instead of NiBr₂, although large amounts of chiral ligand are required. A remarkable achiral ligand effect was observed. Preparation of the chiral catalyst from 6 mol% of Ni(acac)₂, 14 mol% of chiral ligand 2.33 or 2.34, and 7 mol% of 2,2'-bipyridine in acetonitrile raised the enantioselectivity up to 90%. 

\[
\begin{align*}
R-\text{O} & + \text{Et}_2\text{Zn} & \text{Ni(acac)}_2 \text{ (cat.)} & \rightarrow & R-\text{O} \\
\text{2.5-2.13} & \text{CH}_3\text{CN, -30°C} & \text{2.33-2.43 (cat.)} & \rightarrow & \text{43-95% e.e.}
\end{align*}
\]
Comparable yields and enantioselectivities have been reached with nickel catalysts prepared in situ from C$_2$-symmetric bipyridine 2.35$^{35}$ and chiral pyridine 2.36$^{36}$ as reported by Bolm and co-workers and amino alcohol 2.37 as found by Jansen in our laboratory.$^{37}$

The nickel catalysed enantioselective conjugate addition of diethylzinc to chalcone was also performed using optically active β-hydroxysulfoximines as chiral ligands.$^{38}$ The ligand structure was optimised and an e.e. of up to 70% was reached with ligand 2.38.

Figure 2.8 Chiral ligands and complexes used as catalysts in the conjugate addition of diethylzinc to acyclic enones.

Sánchez and co-workers reported the conjugate addition of diethylzinc to enones by homogeneous and supported cationic chiral nickel complexes 2.39 and 2.40, based on proline amide ligands.$^{39}$ Under homogeneous conditions e.e.'s of 75-77% were reached using 5 mol% of catalyst 2.39 at -10$^\circ$C. Although the addition reactions were slower with the supported chiral complexes 2.40, the enantioselectivities were raised to 95%. The relatively high enantioselectivities observed with a chiral ligand-to-nickel ratio of 1, compared to ratios of more than 2 in other studies,$^{32-38,40-42}$ are explained by the fact
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that a single chiral complex is used. Competing catalysis by achiral Ni(acac)$_2$ (or other complexes, see: Eq. 2.16) presumably cannot take place, as often happens in other catalytic reactions. An attractive feature of this system is also the easy removal and recovery of the chiral catalyst.

\[
\text{Ni(acac)}_2 + 2 \text{L}^* = \text{Ni(acac)L}^* + \text{L}^* = \text{NiL}_2^* \quad (2.16)
\]

1,2-Disubstituted arene-chromium complex 2.41 was also employed as chiral ligand in the nickel catalysed 1,4-addition.\(^{40}\) Modest e.e.'s were found strongly depending on amount of catalyst and structure of chromium complex. Recently, two other examples of the nickel catalysed asymmetric conjugate addition of diethylzinc to acyclic enones were reported. With diamine 2.42\(^ {41}\) or amino alcohol 2.43\(^ {42}\) diethylzinc was added to acyclic enones furnishing the 1,4-products in good yields and with e.e.'s ranging from 58-89%.

All reports reveal the following observations:
- The presence of acetonitrile (or another nitrile) as solvent, and presumably as stabilizing ligand to nickel, appears to be essential in all cases.
- Nickel acetylacetonate was found to be the nickel source of choice.
- The enantioselectivity strongly depends on the ligand-to-nickel ratio and the concentration of the in situ prepared chiral catalyst.
- A limited number of alkylzinc reagents and substrates has been successfully used so far in the 1,4-addition reactions described. Various acyclic enones (2.5-2.13, Figure 2.4) give high e.e.'s., however, 2-cyclohexenone (2.2) and α-β-unsaturated esters gave racemic products and low yields.\(^ {36}\)

Soai and co-workers reported that enantioselective conjugate addition to enones also proceed with chiral amino alcohol as catalyst without the use of transition metals, although at much lower rates.\(^ {43}\) After 4 days of reaction time, 1,4-products with e.e.'s of 70-80% were obtained using 25 mol% of 2.34.

Recently, Alexakis and co-workers reported the first example of copper catalysed enantioselective conjugate addition of diethylzinc to 2-cyclohexenone (Eq. 2.17).\(^ {44}\) The use of 10 mol% of CuI and 20 mol% of trivalent phosphorous ligand 2.44 resulted in
an enantioselectivity of 32%. Under the same conditions chalcone gave racemic material.

All these efforts represent a significant advance in the field of catalytic enantioselective conjugate addition reactions, however, there is no general solution to the problem of achieving efficient catalysis for a wide variety of enones.

2.6 Catalytic Michael additions

Chiral metal complexes as catalysts
Carbon-carbon bond formation via Michael additions are most frequently performed under conditions of base catalysis. The conjugate addition of 1,3-dicarbonyl compounds to enones can also be efficiently catalysed by metal complexes. Among the advantages of transition-metal catalysed Michael additions are the high yields that are often found under mild reaction conditions, whereas side reactions, frequently encountered in base catalysed Michael additions, are avoided. Several catalytic Michael additions employing chiral metal complexes have been developed. The Michael donors and acceptors and chiral catalysts are compiled in Figures 2.9 and 2.10, respectively.

Brunner and Hammer were the first to report significant enantioselectivity in a transition-metal catalysed Michael addition. The addition of methyl-1-oxo-2-indanecarboxylate (2.45) to methyl vinyl ketone (MVK, 2.58) in the presence of 3 mol% of a chiral cobalt(II) complex, derived in situ from Co(acac)$_2$ and (1S,1S)-(−)-1,2-diphenylethylenediamine (2.63), provided the Michael product with an enantioselectivity of 66% (Eq. 2.18).

\[
\begin{align*}
\text{2.45} & \quad + \quad \text{2.58} \\
\frac{\text{2.63-2.68(cat.)}}{[\text{Co(acac)}_2 \text{ (cat.)}]} & \quad \rightarrow \quad \text{2.63-2.68(cat.)}
\end{align*}
\]

(2.18)

In further investigations, the Co(acac)$_2$-(−)-1,2-diphenylethylenediamine catalyst was
examined in the Michael addition of unsymmetrical 1,3-dicarbonyl donors under various conditions.\textsuperscript{46} Using MVK, di-t-butyl methylenemalonate (2.62), and acrolein (2.59) as Michael acceptors and Michael donors 2.46 and 2.48, enantioselectivities up to 37\% were reached. Under the reaction conditions the enantioselectivity was almost temperature independent, no racemisation took place and the conjugate addition was irreversible.

Desimoni and co-workers also investigated the model reaction given in Eq. 2.18, employing chiral copper(II) complexes 2.64-2.67.\textsuperscript{47} All copper complexes are based on Schiff base ligands derived from salicylaldehyde and chiral amino alcohols and are presumably dimeric structures. Furthermore there is evidence that H\textsubscript{2}O is bound to the copper atom in these complexes resulting in six coordination around each copper atom. The enantioselectivity strongly depends on the solvent and the chiral catalyst. With catalyst 2.64 enantioselectivities up to 54\% were found in CCl\textsubscript{4}. A negative factor seems to be the ability of the solvent to compete with the chiral ligand for metal complexation. Introduction of a phenyl substituent in the chiral catalyst structure (2.65) drastically reduces the e.e. (7\%). Increase of the rigidity of the catalyst by incorporating an additional hydroxyl group that can act as an axial ligand in 2.66 and 2.67 raised the e.e. to 70\% (based on optical rotations).\textsuperscript{47} Nearly quantitative yields were observed with 1-10 mol\% of copper(II) catalyst at -20°C in CCl\textsubscript{4}.
Michael donors:

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Michael acceptors:

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Figure 2.9 Michael donors and acceptors used in enantioselective Michael additions.

An in situ prepared chiral cobalt(II) catalyst derived from Co(acac)\textsubscript{2} and diamino diol ligand 2.68 was also tested in the addition of 2.45 to MVK (Eq. 2.18). With 4-14 mol% of 2.68, acceptable yields (46-81%) but low e.e.'s (3-38%) were found. This asymmetric catalysis is a property of the metal ligand complex and not of the ligand itself (the free ligand 2.68 appears to favour the opposite absolute stereochemistry). With Ni(acac)\textsubscript{2}, instead of Co(acac)\textsubscript{2}, a lower enantioselectivity was found.

Recently, Ito and co-workers reported a rhodium catalysed enantioselective Michael addition of α-cyanocarboxylates 2.49-2.52 to Michael acceptor 2.58 (Eq. 2.19). The chiral catalyst was prepared in situ from RhH(CO)(PPh\textsubscript{3})\textsubscript{2} and the trans chelating chiral diphosphine ligand 2,2''-bis[1-(diphenylphosphino)ethyl]-1,1''-biferrocene (TRAP, 2.69). Enantioselectivities ranging from 72-84% (for i-propyl-α-cyanocarboxylate) were observed.
The reactions of 2.51 with a large variety of vinyl ketones or acrolein (2.59) proceed with 83-89% e.e. High catalyst efficiency was observed even with 0.1 mol% of 2.69 (84% e.e.) whereas high yields are generally found. Trans chelation of the chiral ligand to rhodium appears to be essential for high e.e.'s as common cis chelating diphosphines, such as BINAP, DIOP, or Chiraphos, resulted in low enantioselectivities. It is proposed that the activated cyanoacetic ester is bound to rhodium through the cyano nitrogen and that in the enolate intermediate the enantioselective carbon-carbon bond formation occurs at the carbon atom rather distant from the metal center (Figure 2.11). Only a concave chiral ligand such as TRAP would effect the remote enantiofacial differentiation. The X-ray crystal structure of trans-[RhCl(CO)((R,R)-(S,S)-n-BuTRAP)], which bears a n-Bu group instead of a Ph group as in 2.69, reveals that rhodium has a nearly planar coordination geometry. The conformation of the ligand is essentially $C_7$-symmetric, and the chloro and carbonyl groups on rhodium, which may be replaced by a prochiral substrate in a catalytic asymmetric reaction, are completely buried in the chiral cavity created by the ferrocenyl backbone and the n-Bu groups.

![Chemical Structures](image)

Figure 2.10 Chiral ligands and complexes used as catalysts in enantioselective Michael additions.

\[
\text{RCO}_2\text{NC} + \text{RCOOR' } \xrightarrow{2.69\text{(cat.)}} \text{RhH(CO)(PPh}_3\text{)}\text{ (cat.)} \text{ benzene, 3°C} \xrightarrow{2.49 - 2.52 \text{ or } 2.58 \text{ or } 2.59} \text{RO} + \text{NC} + \text{RCO}_2\text{R'}
\]

(2.19)
Yamaguchi and co-workers reported the first catalytic asymmetric Michael addition of a simple malonate ion to prochiral enones and enals.\textsuperscript{51} Asymmetric induction was observed when the Michael addition of dimethyl malonate (2.53) to prochiral acceptors catalysed by the lithium salt of L-proline, was carried out in chloroform. Higher catalytic activity and enantioselectivity was attained with the rubidium salt 2.70. Enantioselectivities up to 88% were achieved with 5 mol% of 2.70, malonates (2.54 and 2.55), and various Michael acceptors such as aliphatic and aromatic enones (2.6, 2.60 and 2.61), cyclic enones 2.2 and 2.3, and acrolein. A small amount of water was found to promote the reaction. Yields of Michael products were very low with catalytic amounts of the rubidium salt of N-methyl-L-proline or free L-proline. Thus, both the secondary amine moiety and the metal carboxylate moiety of 2.70 are essential for high catalytic activities. Reversible iminium salt formation to provide chiral Michael acceptors could account for the above asymmetric inductions (Figure 2.12). Independent experiments demonstrated a high reactivity of an unsaturated iminium salt, derived of 2.6 and pyrrolidine, towards malonate addition.\textsuperscript{51}
Figure 2.12 Proposed mechanism in the rubidium catalysed enantioselective Michael addition.

This reversible iminium salt formation, creating differentiation of enantiofaces of the prochiral Michael acceptor has also been applied successfully with ammonium hydroxide 2.71 (Figure 2.10), easily prepared from (S)-proline.\textsuperscript{52} The reaction of malonate 2.53 or 2.56 with cyclic enone 2.1 or 2.2 was conducted in the presence of 1,1,1,3,3,3-hexafluoro-2-propanol to reduce the basicity of the catalyst. The addition products were isolated in moderate yields (50-60\%) and with enantioselectivities ranging from 56-71\% e.e.

Recently, Shibasaki and co-workers reported a chiral lanthanum complex, which is highly effective as catalyst in enantioselective Michael additions of malonates to cyclic enones.\textsuperscript{53} Investigations in order to create an effective catalyst revealed that the lithium-free complex 2.72, derived from 2,2'-dihydroxy-1,1'-binaphthyl (BINOL) (2.25), La(O-i-Pr), and a dialkyl malonate furnishes the corresponding products in high yields and e.e.'s ranging from 75-95\% (Figure 2.13). The mode of addition in the preparation of the ester enolate catalyst 2.72 and the removal of THF and i-PrOH after this preparation is essential for effective catalysis (Eq. 2.20). Remarkably, with MVK and malonate 2.47, affording a product with a stereogenic center on the 4-position, an enantioselectivity of 62\% was achieved.
In subsequent studies the same yields and enantioselectivities were reported by an alkali metal containing trimeric complex, derived of La(O-i-Pr)$_3$, (R)-BINOL (3 equivalents) and NaO-t-Bu (3 equivalents). With this catalyst the reaction of chalcone (2.5) with malonate 2.53 proceed smoothly to give the Michael product in 77% e.e. (93% yield), whereas with catalyst 2.72 only 7% e.e. was found.

Very recently this heterobimetallic catalysis concept was extended with the development of an amphoteric asymmetric complex from aluminium, lithium and (R)-BINOL. Efficient complex preparation from LiAlH$_4$ and two equivalents of (R)-BINOL in THF afforded heterobimetallic catalyst 2.73, which gave excellent yields and enantioselectivities (91-99%) in the Michael addition of several malonates to cyclic enones 2.2 or 2.3. $^{27}$Al NMR studies revealed that the carbonyl group of the enone is coordinated to the aluminum. This mechanistic feature gave the opportunity to trap the Al-enolate with an electrophile. The reaction of cyclopentenone (2.1), diethyl methylmalonate and 3-phenylpropanal in the presence of 10 mol% of 2.73 gave the three-component coupling product as a single diastereomer in 91% e.e. (64% yield) (Eq. 2.21). This is the first example of a catalytic asymmetric tandem Michael-aldol reaction.

Figure 2.13  Proposed mechanism for the asymmetric Michael reaction catalysed by a chiral lanthanum complex.
Chiral amines and crown ethers as catalysts
The use of chiral amines as catalyst in the Michael addition reaction was reported by Långström and Bergson in 1973. The addition of methyl-1-oxo-2-indanecarboxylate (2.45) to acrolein (2.59) using optical active 2-(hydroxymethyl)quinuclidine (2.74, Figure 2.14) provided optical active Michael product (see Eq. 2.18).
Wynberg and co-workers studied the model reaction of the same Michael donor with MVK as Michael acceptor and quinine (2.75) as chiral base (1 mol%). The Michael product is produced in almost quantitative yield with e.e.'s up to 76%, depending on solvent and temperature (Eq. 2.18). Several variations of chiral base, Michael donor and acceptor, and reaction conditions were examined in detail but enantioselectivities exceeding 76% were not reached in these studies.
Several attempts were reported to facilitate removal of the chiral catalyst from the reaction mixture by attaching it to a polymer. With alkaloids 2.75, 2.77, and 2.78 anchored to cross-linked polystyrene or co-polymerized with acrylonitrile the Michael additions given in Eq. 2.18 proceed with low and moderate e.e.'s, respectively. Insertion of spacer groups between the alkaloid and the polymer backbone improves the enantioselectivity to 65%. This is almost the same value as was found in the reaction with non-polymer bound alkaloid. When the model reaction (Eq. 2.18) was performed under high pressure lower e.e.'s were found.
Figure 2.14  Chiral amines and crown ethers used in Michael additions.

The model reaction was also performed under phase transfer conditions. With quartenary ammonium halides, derived from methionine, the reaction is sluggish and hardly enantioselective.\textsuperscript{64} Significant improvements were achieved with [p-(trifluoromethyl)benzyl]-chinchoniniumbromide (2.78) as phase transfer catalyst and 2-propyldanone as Michael donor,\textsuperscript{65} and under solid-liquid phase transfer conditions in presence of quaternary ammonium salts, 2.80-2.82, derived from N-methylephedrine (a typical example is given in Eq. 2.22).\textsuperscript{66}
Higher enantioselectivities have been reached using chiral catalysts prepared by complexation of a base to a chiral crown ether. Cram and Sogah found that with 4 mol% of a bis-β-naphthol derived optically active crown ether \(2.83\) (Figure 2.14) and potassium t-butoxide as the base, the Michael product (Eq. 2.18) was isolated in 48% yield with an e.e. of 99%. crown ether \(2.84\) was used similarly in the reaction of methyl acrylate and methyl 2-phenylpropionate or methyl phenylacetate (Eq. 2.23). The highest e.e.'s in the latter reactions were achieved with potassium amide as base (83% and 65% e.e., respectively). In both cases the R crown ether gave the S product.

In the presence of KO\(_t\)-Bu, crown ethers \(2.83\) and \(2.84\), were also used as chiral catalyst in the anionic (Michael type) polymerization of methacrylate esters to give highly isotactic helical polymers. Following these fascinating reports, several groups have been investigated other chiral crown ethers as catalysts in the reaction given in Eq. 2.23. Enantioselectivities did not rise above 81%. A remarkable high enantioselectivity of 79% was achieved with simple \(C_2\)-symmetric chiral crown ether \(2.86\) derived from 2S,3S-butanediol. With chiral crown ether \(2.85\), Yamamoto and co-workers investigated the Michael addition of methyl phenylthioacetate to cyclopentenone to give the Michael product in 60% yield with an e.e. of 41% (Eq. 2.24). With crown ether \(2.87\) Koga and co-workers were able to enhance the enantioselectivity to 68% in this reaction.
2.7 Nitroalkane additions

In recent years, Michael addition reactions of nitroalkanes to activated alkenes have attracted considerable attention in part due to the availability of various synthetic methods for the conversion of the nitro group to other functional groups. Only a few enantioselective nitromethane additions to enones catalysed by alkaloids and derivatives have been reported. With quaternary salts derived of quinine or N-methyllephedrine (2.76, 2.79-2.81, Figure 2.14) as chiral phase transfer catalysts and excess of inorganic salts (KF, NaOH or KOt-Bu) enantiomeric excesses up to 26% were reached in the addition of nitromethane to chalcone (Eq. 2.25). With the free alkaloids as chiral bases no reaction takes place in aprotic solvents. In methanol addition takes place although without enantioselectivity.

Under high pressure (900 MPa) both quinine (2.75) and quinidine (2.77) (10 mol%) catalyse the nitromethane addition in aprotic solvents like toluene, with high conversion and e.e.’s up to 60%. These results shows that high pressure is actually advantageous in performing sluggish asymmetric reactions composed of rather inert reactants and/or poor catalysts.

Botteghi and co-workers reported the first example of a transition-metal catalysed enantioselective nitroalkane addition to enones (Eq. 2.25). The catalyst was prepared...
in situ from Ni(acac)_2 and proline-derived ligands 2.88-2.90. Using a large excess of nitromethane, enantioselectivities up to 17% where reached although long reaction times are required. With benzylideneacetone slightly higher e.e.'s (24%) but low yields were found. A decrease of Michael donor-to-acceptor ratio appears to increase the asymmetric induction. With equimolar amounts of donor and acceptor the chemical yield of the Michael product is rather low, but an enantioselectivity of 61% is found (ligand 2.89). The observed increase in e.e. might well be a solvent effect. An increase in solvent polarity (nitromethane vs benzene) produces a decrease in stereoselectivity in the same reaction catalysed by alkaloid bases under phase transfer conditions.

Asymmetric catalysis is confirmed to be a property of metal complexes in this case as the ligands alone do not catalyse the reaction.

Yamaguchi and co-workers noted a reaction of 2-nitropropane and 2-cyclohexenone (2.2) or (E)-3-penten-2-one (2.61) in the presence of 5 mol% of rubidium salt 2.70. The products were obtained with yields of 61% and 48% and e.e.'s of 58% and 69%, respectively.

2.8 Miscellaneous

Two additional successful approaches to catalytic asymmetric Michael addition need to be mentioned, which use chiral Lewis acids as catalysts. Mukaiyama and co-workers used a chiral tin complex derived in situ from tin(II) triflate and chiral diamine 2.91 in the Michael addition of trimethylsilyl enethiolate to enones (Eq. 2.26). When the trimethylsilyl enethiolate was added slowly to the reaction mixture, in order to suppress the competing uncatalysed addition, enantioselectivities up to 70% were reached. It is proposed that metal exchange of tin and silicium initially takes place to generate a chiral tin(II) enethiolate and Me_SiOTf. Activation of the enone by Me_SiOTf induces the Michael addition of the chiral tin(II) enethiolate along with the regeneration of the tin(II) triflate-diamine complex.
Catalytic asymmetric Michael additions of morpholine derived enamines to methyl(E)-4-oxo-4-(2-oxo-1,3-oxazolidin-3-yl)-2-butenoate with modest yields but promising e.e.'s were found by Narasaka and co-workers (Eq. 2.27). The chiral catalyst is prepared in situ from Cl₂Ti(Oi-Pr)₂ and (2R,3R)-1,4-diol, 2.92, derived from tartaric acid. The course of the titanium-catalysed addition reaction of enamines with unsaturated acid derivatives was strongly depending on the enamine structure. Contrary to the Michael reaction of the enamines given above, the reactions of 2,2-disubstituted enamines with the same Michael acceptor were found to afford optically active cyclobutanes. The in situ prepared chiral catalyst was also used successfully in Diels-Alder and [2+2] cycloadditions, ene reactions, and hydrocyanations.

\[ \text{R} = \text{Ph, t-Bu} \]

\[ \text{R} = \text{Ph, t-Bu} \]

\[ \text{R} = \text{Ph, t-Bu} \]

\[ \text{R} = \text{Ph, t-Bu} \]

\[ \text{R} = \text{Ph, t-Bu} \]

2.9 Conclusions

The current stage of enantioselective synthesis of β-substituted carbonyl compounds using chiral catalysts has been reviewed in this chapter. Remarkable progress has been made in the last few years on the enantioselective synthesis of β-substituted carbonyl compounds by conjugate addition catalysed by chiral metal complexes. Except for an early report by Brunner on cobalt-catalysed Michael additions, the first successful enantioselective conjugate addition reactions catalysed by metal complexes appeared in 1988. A number of examples are currently known of both Michael type additions and 1,4-additions of organometallic reagents catalysed by chiral metal complexes with enantioselectivities exceeding 80%. The large variety of chiral metal complexes and ligands that have shown modest enantioselectivities are the stepping stones for the development of highly selective catalysts in the near future.
A wealth of information has already been gathered on the factors effecting catalytic activity and selectivity. A picture emerges of conjugate addition reactions being often extremely delicate and complex processes, in particular due to the appearance of various catalytically active complexes (in equilibrium) during the reaction and the sensitivity to the conditions of the reaction. The scope of organometallic reagents, Michael donors, and enones in these enantioselective processes has been limited so far. With a few exceptions model reactions have been studied only. It is evident that the development of highly selective catalysts for conjugate addition with a broad scope is a major challenge in current asymmetric synthesis.

2.10 References


59. For related enantioselective Michael addition o-f-3,4-dimethoxybenzyl cyanide to several enones with e.e. < 11%, see: Brunner, H.; Zintl, HMonatsh. Chem. 1991, 122, 841. For conjugate cyanide addition to enones with e.e. < 45%, see: Dehmlow, E.V.; Sauerbier, CLiebig's Ann. Chem. 1989, 181.


