Synthetic applications of the catalytic asymmetric 1,4-addition
Naasz, Robert

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

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

Publication date:
2002

Citation for published version (APA):
Naasz, R. (2002). Synthetic applications of the catalytic asymmetric 1,4-addition. [Thesis fully internal (DIV), University of Groningen]. s.n.

Copyright
Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the “Taverne” license. More information can be found on the University of Groningen website: https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment.

Take-down policy
If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): http://www.rug.nl/research/portal. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.
Chapter 2

The catalytic enantioslective 1,4-addition of organometallic reagents: copper catalyzed addition of organozinc reagents and related approaches

2.1 Introduction

The discovery of the successful phosphoramidite ligand (S,R,R)-L1 as described in Section 1.3, has led to an increasing interest in the conjugate addition of organometallics. The attention of research in the field of enantioslective 1,4-additions was focussed on the copper catalyzed 1,4-addition of organozinc reagents. In the present chapter, the development of new ligands and catalysts for the copper catalyzed enantioslective 1,4-addition of organozinc reagents and their application from 1997 onwards, in our research group and by others, is reviewed.1 Additionally, the information known to date about the mechanism of these 1,4-additions is summarized in Section 2.3. Finally, the recent development of another catalytic system, the highly enantioslective rhodium-BINAP catalyzed 1,4-addition of organoboronic acids developed by Hayashi et al., is discussed briefly (Section 2.4).

2.2 Copper catalyzed enantioslective 1,4-addition of organozinc reagents

As mentioned in the introduction, a variety of successful catalytic systems have been developed since 1997. The majority of the ligands in use are based on phosphorus, such as phosphoramidites (PO₂N, Section 2.2.1), phosphites (PO₃, Section 2.2.2), phosphonites (PO₂C, Section 2.2.3) and phosphines (PC₃, Section 2.2.4), and other phosphorus containing ligands (Section 2.2.5), but other ligands have also been applied; they are discussed in Section 2.2.6.

2.2.1 Phosphoramidites

As described in the previous chapter, the copper catalyzed 1,4-addition to 2-cyclopentenone (2.1) in the presence of (S,R,R)-L1 resulted in a low enantioslectivity of only 10% ee.2 Therefore, one of the priorities in our group was to develop phosphoramidite ligands that would display high enantioslectivity in the 1,4-addition to 2-cyclopentenone. TADDOL³ based phosphoramidite (R,R)-2.4 (Figure 2.1) was found to give a moderate ee of 37% in the
tandem 1,4-addition-aldol reaction (Scheme 2.1). The reactions were carried out in the presence of benzaldehyde to prevent undesired oligomerization by in situ trapping of the reactive zinc enolate that is formed by the 1,4-addition of Et₂Zn to 2.1.

![Scheme 2.1 Tandem 1,4-addition-aldol reaction on 2-cyclopentenone.](image)

The addition of 4 Å molsieves to the reaction mixture had a beneficial effect on the ee, which went up from 37% to 62%. The exact nature of the influence of the molecular sieves is not understood.

![Figure 2.1 Phosphoramidite ligands.](image)

Initial experiments with BINOL based phosphoramidites revealed a dramatic increase in the ee obtained in the 1,4-addition to 2-cyclopentenone when going from monodentate ligands to the structurally related C₂-symmetric bidentate ligands. The preparation and testing of a variety of such bidentate ligands, e.g. 2.5 and 2.6, eventually led to an ee of 83% for 2.3, obtained with (S,S)-2.5 in the presence of 4 Å molsieves (79% ee without molsieves). A different approach to solve the problem of the moderate ee’s obtained in the 1,4-addition to cyclopentenones is modification of the substrates. It was found that the use of cyclopenten-3,5-dione monoacetals such as 2.7 as substrates led to very satisfactory ee’s ranging from 87% to 97%, with the use of ligand (S,R,R)-L1. The usefulness of these
substrates has been demonstrated by the total synthesis of prostaglandin E\textsubscript{1} methyl ester (2.9) in seven steps (Scheme 2.2).

![Scheme 2.2 Total synthesis of PGE\textsubscript{1} methyl ester (2.9).](image)

Further variation of the amine moiety and modification of the BINOL part led to the synthesis of a variety of phosphoramidite ligands, which were tested on both cyclohexenone and various acyclic enones.\textsuperscript{8} However, (S,R,R)-L\textsubscript{1} remains the best phosphoramidite ligand for cyclic enones and the diisopropyl BINOL-phosphoramidite 1.34\textsubscript{b} (Chapter 1) generally gives the best results with chalcones.

The copper-phosphoramidite catalyst based on L\textsubscript{1} was also tested on other substrates, in our group and by others. Sewald and Wendisch successfully used both (R,S,S)-L\textsubscript{1} and (S,S,S)-L\textsubscript{1} in the 1,4-addition to nitroolefins, obtaining ee’s up to 86\% (Scheme 2.3).\textsuperscript{9}

![Scheme 2.3 1,4-Addition to nitroolefins.](image)

Related classes of substrates, \(\alpha,\beta\)-unsaturated nitroesters and nitrocoumarins, were investigated in our laboratory and with the use of (S,R,R)-L\textsubscript{1} ee’s of up to 92\% were reached.\textsuperscript{10} Also very successful were the enantioselective 1,4-additions to a variety of cyclohexadienones and related compounds.\textsuperscript{11} An elegant feature of these substrates, e.g. 2.12, is the possibility of performing two sequential 1,4-additions, in which the stereochemical outcome of the second 1,4-addition is solely dependent on the enantiomer of L\textsubscript{1} that is used in each step and is not influenced by the presence of stereogenic centres at the 4- and 5-position of 2.13 (Scheme 2.4). Phosphoramidite (S,R,R)-L\textsubscript{1} was employed also by Alexakis \textit{et al.} for the catalytic asymmetric synthesis of muscone in 75\% ee (see also Scheme 1.8, Chapter
1) and the 1,4-addition to acyclic enones.\textsuperscript{12} They also used (S,R,R)-L1 in enantioselective tandem 1,4-addition-electrophile trapping reactions.\textsuperscript{13}

![Scheme 2.4](image)

**Scheme 2.4 Sequential 1,4-additions to cyclohexadienone 2.12.**

Following the initial reports,\textsuperscript{2a,14} a variety of phosphoramidites has been prepared and tested in the 1,4-addition to various substrates. Some of these phosphoramidite ligands are depicted in Figure 2.2.

![Figure 2.2](image)

**Figure 2.2 Phosphoramidite ligands.**
Phosphoramidite (S,S)-2.15 and related ligands were recently reported by Alexakis et al. They claim that the atropoisomerism of the biphenol unit is induced by the chiral amine, although this claim is not supported by experimental proof. An advantage of these ligands is that the biphenol used for the synthesis of (S,S)-2.15 is cheaper than enantiomerically pure BINOL and for some substrates higher enantioselectivities are obtained than with (S,R,R)-L1. Alexakis also reported the synthesis and use of a variety of TADDOL based phosphoramides and reached the same conclusion that Erik Keller in our group had previously, that bulky substituents on the nitrogen in these ligands are detrimental for high enantioselectivities. The best result was indeed obtained with the sterically least hindered (R,R)-2.16, giving 49% ee in the 1,4-addition of diethylzinc to benzalacetone. Quinoline based phosphoramidite (S_oR_c)-2.17 was reported by Faraone et al. and was tested in the 1,4-addition of Et_2Zn to 2-cyclohexenone providing a maximum ee of 70%. Waldman et al. reported on the synthesis of C_2-symmetric phosphoramidite (R,R)-2.18 and the related monodentate (R)-2.19. Of these two, the bidentate (R,R)-2.18 proved to be the superior ligand for cyclic enones, giving 82% ee in the 1,4-addition of Me_2Zn to 2-cyclohexenone and 2-cycloheptenone. For acyclic substrates such as chalcone, (R)-2.19 gave slightly better results, reaching 82% ee in the 1,4-addition of n-Bu_2Zn against 60% ee as obtained with (R,R)-2.18. Chan et al. reported on the use of a diisopropylamino phosphoramidite with a H_8-binaphthoxy moiety as the chiral backbone instead of BINOL with ee’s up to 88%. 8,8’-BINOL derived phosphoramidites and their application in the copper catalyzed enantioselective 1,4-addition have also been reported, albeit with moderate enantioselectivities of up to 50%.

2.2.2 Phosphites

The first successful chiral phosphite ligands were reported by the group of Pfaltz in 1997. Using phosphinoxazoline ligands (R,S)-2.20a and b, ee’s up to 96% were obtained in the Cu(OTf)_2 catalyzed 1,4-addition of Me_2Zn to 2-cyclohexenone and 50% ee in the addition of Et_2Zn to chalcone (Figure 2.3).

![Phosphite Ligands](image-url)
Very encouraging were the results obtained with 2-cyclopentenone as the substrate, for which an ee of 72% was obtained with \((R,S)-2.20b\). Further modification of these ligands, and, especially, introduction of bulky substituents at the 3,3’ position of the BINOL backbone, led to the synthesis and testing of, among others, \((R,S)-2.20c\) and \((R,S)-2.20d\).\(^{22}\) \((R,S)-2.20c\) gave an impressive ee of 94% in the 1,4-addition to 2-cyclopentenone and high enantioselectivities were obtained in the 1,4-addition of \(\text{Et}_2\text{Zn}\) to 2-cyclohexenone (90%), 2-cycloheptenone (94%) and chalcone (87%).

Alexakis \textit{et al.} reported on a series of phosphites based on tartrate,\(^{23}\) TADDOL,\(^{24}\) and BINOL.\(^{12}\) The tartrate phosphites gave only moderate results, the maximum ee being 65% obtained with benzalacetone as the substrate. TADDOL based phosphite \(2.21\) was the most successful one of the tested series, giving 96% ee in the addition of \(\text{Et}_2\text{Zn}\) to 2-cyclohexenone, although only racemic material was obtained with benzalacetone as the substrate. The best result obtained with the corresponding BINOL phosphite \(2.22\) was 87% ee in the 1,4-addition of \(\text{Me}_2\text{Zn}\) to 2-cyclopentadecenone, producing muscone (see Chapter 1).

The BINOL based phosphites \((S,S)-2.23\) and \((S,S,S)-2.24\) have been reported by Chan \textit{et al.}\(^{25}\) (Figure 2.4). These phosphites were especially successful in 1,4-additions to 2-cyclopentenone, an ee of 89% being reached using \((S,S)-2.23\). An interesting effect of the temperature of the reaction mixture on the enantioselectivity was observed. At 20 °C a higher ee (88%) was obtained than at 0 °C (84%) and at –20 °C only moderate conversion with an ee of 8% was found. The optimum temperature seems to be 10 °C resulting in the aforementioned 89% ee. Other cyclic enones also gave good results with these ligands with ees up to 90% for 2-cyclohexenone, but chalcone only gave a maximum ee of 17%. Chan \textit{et al.} were the first to report the copper catalyzed enantioselective 1,4-addition of organozinc reagents to \(\alpha,\beta\)-unsaturated lactones using the same phosphite ligands (Scheme 2.5).\(^{26}\) The 1,4-addition of \(\text{Et}_2\text{Zn}\) to the 6-membered lactone \(2.25b\) proceeded with 92% ee and a moderate ee of 56% was obtained for the 5-membered lactone \(2.25a\).
The catalytic enantioselective 1,4-addition of organometallic reagents

![Diagram](image)

**Scheme 2.5 Enantioselective 1,4-addition to lactones using (S,S)-2.23.**

Pâmies *et al.* reported a series of sugar derived phosphites. Initially they synthesized phosphites based on ribose and different biphenols but the ee’s obtained were moderate, with a maximum ee of 53% in the 1,4-addition of Et₂Zn to 2-cyclohexenone. Further modification led to the synthesis of 2.27, a very bulky phosphite that gave 81% ee in the 1,4-addition of Et₂Zn to 2-cyclohexenone at 0 °C in CH₂Cl₂. With this ligand they observed a high initial turnover frequency of 1200 h⁻¹ and full conversion was reached within 5 min using 1 mol% of ligand and Cu(OTf)₂.

![Figure 2.5 Ribose derived phosphite 2.27 and phosphine-phosphite 2.28.](image)

Together with the group of Van Leeuwen they also reported the use of phosphine-phosphite ligands, e.g. 2.28, in the catalytic enantioselective 1,4-addition. Although these ligands gave high turnover frequencies, very low enantioselectivities were obtained in the 1,4-addition of Et₂Zn to 2-cyclohexenone with a maximum ee of 22%. Better results were obtained using a Et₃Al/Cu(MeCN)₄BF₄ system instead of Et₂Zn/Cu(OTf)₂, reaching 62% ee in the addition to 2-cyclohexenone.

**2.2.3 Phosphonites**

Only a few successful applications of chiral phosphonites in enantioselective 1,4-additions have been reported. Interestingly, all the phosphonite ligands reported so far were initially prepared for applications in other catalytic enantioselective reactions. Reetz *et al.* prepared
the C₂-symmetric ferrocene based phosphonite 2.29 that was originally successfully applied in the rhodium catalyzed hydrogenation. (Figure 2.6).²⁹ When applied in the 1,4-addition of Et₂Zn to 2-cyclohexenone, an impressive ee of 96% was obtained.³⁰ Unfortunately, no systematic screening of different substrates has been reported, although 98% ee has been reported for the 1,4-addition to lactone 2.25b.³¹

![Chiral phosphonite ligands](image)

**Figure 2.6 Chiral phosphonite ligands.**

Alexakis *et al.* described the successful application of TADDOL phosphonite 2.30, used originally in catalytic enantioselective hydrosilylation and hydroformylation reactions,³² in the 1,4-addition to nitroolefines (see also Scheme 2.3).³³ Ee’s ranging from 31% to 86% were reached using various nitroolefins. In contrast, the use of (S,S)-2.30 in the 1,4-addition to chalcone and 2-cyclohexenone resulted in 7% ee and 54% ee, respectively.¹⁶

In a cooperation between us and the group of Pringle, the BINOL and biphenanthal based phosphonites with various exocyclic substituents previously used in the catalytic enantioselective hydrogenation,³⁴ were tested in the 1,4-addition of Et₂Zn to 2-cyclohexenone and chalcone.³⁵ Only moderate results were obtained using 2-cyclohexenone as a substrate with a maximum ee of 41%, but an ee of 82% was obtained in the 1,4-addition of Et₂Zn to chalcone using (S)-2.31. With the related phenanthrol phosphonite (S)-2.32, 80% ee was reached under the same conditions. The phosphonites were also tested in the 1,4-addition to nitroolefins, but in contrast to TADDOL based phosphonite 2.30, only low enantioselectivities were observed (<20% ee).³⁶
2.2.4 Phosphines

In 1997 Alexakis reported on the accelerating effect that both alkyl and aryl phosphines had on the copper catalyzed 1,4-addition of organozinc reagents. A wide variety of commercially available diphosphines were tested but no satisfactory levels of enantioselectivity were obtained (0-44% ee) on either cyclic or acyclic enones.

![Figure 2.7 Chiral phosphines used in the enantioselective 1,4-addition.](image)

The first really successful application of phosphines was reported in 1999 by Imamoto et al. In the presence of 1 mol% Cu(OTf)₂ and 1 mol% 2.33a in toluene at −80 °C, 83% ee was obtained in the 1,4-addition of Et₂Zn to 2-cyclohexenone. For 2-cycloheptenone and chalcone, phosphine 2.33b gave better results with 97% and 71% ee, respectively. A milestone was reached by Zhang et al. using (S)-2.34a and b. They employed these ligands for the first time and obtained high ee’s (>90%) with both cyclic and acyclic enones with the same catalytic system. Ee’s of 98% were reached, also for the first time, in the 1,4-addition to chalcones. In the 1,4-addition to 2-cyclohexenone, 91% and 92% ee were obtained using (S)-2.34a and (S)-2.34b, respectively. For chalcones (S)-2.34b clearly was the superior ligand, giving 96% ee with chalcone and 98% ee with 4-methoxy substituted chalcone. Morimoto et al. reported on the use of several new P,N ligands of which (S)-2.35 was the most successful, giving 91% ee in the 1,4-addition of Et₂Zn to 2-cyclohexenone. (S)-2.36 was reported by Tomioka et al., but only moderate results were obtained in the 1,4-addition to 2-cyclohexenones with ee’s ranging from 7-64%. Recently, the group of Hoveyda reported the use of highly modular peptide-based phosphines in the copper catalyzed 1,4-addition of organozinc reagents (Figure 2.8).

![Figure 2.8 Modular peptide-based phosphines.](image)
Excellent results with ee’s of 98% or higher were obtained with the use of a catalyst prepared in situ from \((S,S)-2.37\) (2.4 mol%) and Cu(OTf)\(_2\cdot\)C\(_6\)H\(_6\) (1 mol%) in toluene for 2-cyclopentenone, 2-cyclohexenone, and 2-cycloheptenone with different organozinc reagents. Unfortunately, 1,4-additions to acyclic enones using these phosphine ligands have not been reported as yet. Since the phosphines are constructed from two or three amino acids, numerous variations in ligand structure are possible using readily available compounds. To demonstrate this, the problem of the somewhat lower enantioselectivity (72% ee) using \(i\)-Pr\(_2\)Zn in the 1,4-addition to 2-cyclohexenone in the presence of \((S,S)-2.37\) was addressed. By using a positional optimization strategy, \((S,S)-2.38\) was identified as a superior ligand, giving 91% ee in the addition of \(i\)-Pr\(_2\)Zn. The authors mention that by carrying out a complete ligand screening, a different optimal chiral phosphine construct may emerge for each particular enone. Additionally, a synthetic application of this highly enantioselective 1,4-addition is presented in the same paper; the total synthesis of clavularin B (2.40, Scheme 2.6).\(^{42}\) The zinc enolate resulting from the 1,4-addition of Me\(_2\)Zn to 2-cycloheptenone was quenched with 4-iodo-1-butene in the presence of HMPA yielding 2.39 with 97% ee. This compound was subsequently converted to clavularin B (2.40) in three steps.

![Scheme 2.6 Catalytic enantioselective synthesis of clavularin B (2.40).](image)

### 2.2.5 Other phosphorus containing ligands

Aminophosphines \((S,S)-2.41a\) and \(b\) were reported by Tomioka et al. and tested in the 1,4-addition of Et\(_2\)Zn to 2-cyclohexenones (Figure 2.9).\(^{44}\) Only moderate ee’s were obtained, ranging from 40 to 70% and 5 mol% of Cu(OTf)\(_2\) and 10 mol% of ligand were required to reach these enantioselectivities.

![Figure 2.9 Chiral phosphorus ligands.](image)
Quinoline based phosphane ligand (S)-2.42 was reported by Buono et al.\textsuperscript{45} Although only moderate ee's were reported, an interesting effect of water was observed. Using similar conditions the ee could be raised from 7\% to 61\% by adding a small amount of water. Since the addition of Zn(OH)\textsubscript{2} also has a beneficial effect, this is probably formed \textit{in situ} by hydrolysis of Et\textsubscript{2}Zn and acts as a Lewis acid, although the precise role of water has not been elucidated. Note that the beneficial effect of a trace of water might also be an explanation for the higher enantioselectivity observed in the 1,4-addition to 2-cyclopentenone in the presence of (R,R)-2.4 and molecular sieves, which may contain some water (Section 2.2.1).

### 2.2.6 Non-phosphorus containing ligands

Although most of the attention in the development of new ligands for the copper catalyzed enantioselective 1,4-addition has been devoted to phosphorus ligands, due to the high affinity of these soft Lewis bases for copper, some interesting and successful chiral ligands that do not contain phosphorus have been developed. Following initial reports by Noyori et al.\textsuperscript{46} about the copper catalyzed 1,4-addition in the presence of achiral sulfonamides, Sewald reported the first enantioselective version of this reaction in 1997, using various chiral sulfonamides.\textsuperscript{47} Although a clear ligand accelerating effect was observed, low enantioselectivities were obtained in the 1,4-addition of Et\textsubscript{2}Zn to 2-cyclohexenone (ee < 30\%). Tomioka \textit{et al}. also had little success in the application of chiral disulfonamides, reporting a maximum ee of 28\%.\textsuperscript{44}

Successful examples of sulfonamide ligands for the copper catalyzed asymmetric 1,4-addition to alkenones were found by Gennari \textit{et al}. by high-throughput screening of a parallel library of ligands.\textsuperscript{48}

![Figure 2.10 Chiral Schiff base sulfonamide ligands.](image-url)

A variety of sulfonamides with the general structure 2.43 was prepared by condensation of salicylaldehydes with enantiomerically pure β-amino sulfonamides (which in turn were prepared by reaction of different primary amines with sulfonylchlorides) using solution-phase parallel synthesis and solid-phase extraction techniques. Through screening of a library of 100 ligands, 2.44 was identified as the best ligand for the 1,4-addition of Et\textsubscript{2}Zn to 2-cyclohexenone and 2-cycloheptenone, with 90\% and 91\% ee, respectively. Sulfonamide 2.45 was identified as the best ligand to promote the 1,4-addition of Et\textsubscript{2}Zn to 2-cyclopentenone with an ee of 80\%. Enantioselective 1,4-addition to chalcone proved to be more difficult. A
maximum ee of 50% was obtained by screening a large library of ligands. The same procedure was applied also to nitroalkenes as substrates and a chiral sulfonamide ligand was identified that gave a maximum ee of 58%.49 Surprisingly high ee’s were obtained by Pàmies et al. using a very simple sugar-based thiol ligand, with ee’s up to 62% in the 1,4-addition of Et₂Zn to 2-cyclohexenone.50 Woodward et al. reported on the use of BINOL-derived thiols displaying up to 77% ee in the 1,4-addition to acyclic enones.51 Alexakis and Mangeney recently reported the use of diaminocarbenes as ligands in the copper catalyzed 1,4-addition, although the obtained enantioselectivities were only moderate with a maximum ee of 51%.52

2.2.7 Other applications
As mentioned in Section 2.2.3, many ligands originally intended for application in other catalytic enantioselective processes have successfully been used in the catalytic enantioselective 1,4-addition. But the reverse is also true and ligands used in the 1,4-addition are being used in other reactions with much success. Examples are the use of phosphoramidites in hydrogenations,53 Heck reactions,54 and S_N2’ substitutions55 in our group and by others. Phosphoramidites also found successful application in the ring opening of vinylic epoxides and related compounds.56 Pàmies et al. reported extensively on the use of their phosphite and phosphine ligands in hydrogenation57 and hydroformylation reactions.58 Reports on the phosphoramidite catalyzed borane reduction of ketones with complete enantioselectivity have also appeared, although one of the papers was subsequently retracted.20,59

2.3 Mechanism of the copper catalyzed 1,4-addition of diorganozincs
The mechanism of the 1,4-addition of cuprates and the structure of cuprates in solution has been investigated extensively but remains a subject of considerable debate.60 Different mechanisms have been proposed and rejected, such as the single electron transfer (SET) mechanism proposed by House et al.61 and the 1,2-addition mechanism over the C=C double bond.62 Extensive theoretical studies by Nakamura, in combination with experimental data of others, have led to the proposal of the reaction mechanism shown in Scheme 2.7 for the 1,4-addition of cuprates to enones.60 The central feature of this mechanism is the 3-cuprio(III) enolate (CPop) which has an open, dimeric structure. In this complex copper/olefin (soft/soft) and lithium/carbonyl (hard/hard) interactions are achieved. The three limiting structures of the intermediate CPop are shown in the box in Scheme 2.7. Stable copper-enone π-complexes have been observed using NMR techniques by several research groups.63 The relative stability of the trialkylcopper species can be understood with the “3-cuprio(III) enolate” structure where the internal enolate anion acts as a strong stabilizing ligand. The rate determining step of the reaction (to form TScc) is the C-C bond formation caused by
The catalytic enantioselective 1,4-addition of organometallic reagents

reductive elimination of Cu$^{III}$ to Cu$^{I}$. This proposed mechanism is in accordance with kinetic data obtained previously by Krauss and Smith, who showed that the 1,4-additions of cuprates are first-order in both cuprate dimer and enone.

Scheme 2.7 Mechanism for the 1,4-addition of cuprates as proposed by Nakamura.

It must be kept in mind that this mechanism is proposed for cuprates, i.e. with Li as the counter cation, and it is not clear whether these results can be readily transposed to the copper catalyzed 1,4-addition of organozinc reagents where zinc is the counter cation. Interestingly, Nakamura et al. suggest, on the basis of their calculations on cuprates (!), that the role of the effective chiral ligands in the 1,4-addition of organozinc reagents is to selectively accelerate reductive elimination of one of the diastereomeric CPop intermediates, through complexation of the phosphorus moiety of the ligand to the Cu$^{III}$ in TScc (Scheme 2.8). Note that this view is different from previous suggestions that focus on the copper-olefin complexation step as the crucial face-selective step.

Scheme 2.8 Enantioselection through selective reductive elimination.
In contrast to the large amount of research related to the mechanism of the 1,4-addition of cuprates, little is known about the mechanism of the copper catalyzed 1,4-addition of organozinc reagents. The only extensive mechanistic studies were published by Noyori et al. dealing with achiral sulfonamide ligands (vide infra).67 In 1997, the catalytic cycle depicted in Scheme 2.9 was postulated by our group,2,68 based on results obtained so far. After in situ reduction of Cu(II) to Cu(I),69 a copper ethyl species (L₂CuEt) is formed by alkyl transfer from zinc to copper.70 The proposal of participation of two phosphoramidite ligands in the catalytically active complex was based on the optimum ligand-to-copper ratio of 2 and the observation of nonlinear effects.2,8 Indication for the existence of an electron rich CuEt species was later provided by Chan et al.25a Recording a ³¹P-NMR spectrum of a 2:1 solution of (S,S,S)-2.24 and Cu(OTf)₂ in toluene—d₈, a peak was observed at δ 149.0 ppm (free 2.24) and a peak at 231.6 ppm, which they ascribe to a (S,S,S)-2.24-Cu(OTf)₂ species. Upon addition of an excess of Et₂Zn, the peak at 231.6 ppm disappeared quickly and a new peak at δ 124.0 was observed which was ascribed to an Et-Cu¹ complex containing a molecule of (S,S,S)-2.24.

Scheme 2.9 Proposed catalytic cycle.

Complexation of the alkylzinc fragment to the carbonyl of the enone and formation of the π-complex of the copper with the enone results in 2.46, that might be compared with CPop in Scheme 2.7. Subsequent addition of the ethyl group, possibly via a 3-cuprio(III) enolate (see Scheme 2.7) generates the zinc enolate 2.47. After reaction the zinc enolate is released and the copper catalyst (L₂CuX) is available for the next catalytic cycle. Release of the zinc enolate from the catalyst is facilitated by the formation of a stable dimeric structure of the zinc enolate 2.47 in toluene, as demonstrated by Noyori using cryoscopic molecular weight measurements.67
Noyori et al. also reported extensive kinetic studies using a CuCN/sulfonamide 2.48 catalyst, following the reaction by measuring the intensity of the C-O stretching band of the zinc enolate in the IR-spectrum. The reaction turned out to proceed with first-order kinetics in both Et₂Zn and 2-cyclohexenone and also in CuCN and sulfonamide 2.48. These studies led to the conclusion that this particular catalytic system can be simply viewed as a bisubstrate-uniproduct system. The catalyst reversibly captures Et₂Zn and 2-cyclohexenone to form a 2.48/Et₂Zn/cyclohexenone complex (A, Figure 2.11, compare with CPop in Scheme 2.7), in which alkyl transfer occurs (B, Figure 2.11). The catalyst/product complex formed releases the product thus regenerating the catalyst and completing the cycle. Because the reaction proceeds with first-order kinetics in Et₂Zn and 2-cyclohexenone, the turnover rate is only limited by the alkyl-transfer step and not the product releasing step. Since the sulfonamide 2.48 is structurally and electronically very different from phosphoramidites and other phosphorus containing ligands, different kinetics could be observed with these ligands, but kinetic studies are required to establish this.

![Figure 2.11 Sulfonamide 2.48 and proposed intermediates in the catalytic cycle (A and B).](image)

In line with observations in our group, Noyori et al. also found that Me₂Zn is considerably less reactive than Et₂Zn. In a competition experiment using equimolar amounts of both zinc reagents less than 10% of methylated product was formed. To study the influence of different possible conformers of enone systems, s-trans, s-cis, and flexible enones also were compared. The results led to the conclusion that the reactivity of these substrates increases going from s-cis (e.g., 2.49) to flexible (e.g., 2.50) to s-trans (e.g., 2.51), the relative initial rate of reaction with a CuCN/2.48 system at 0 °C being 1 : 4 : 80. It should be mentioned that comparison of 2.49 with the other two purely based on its conformation may not be appropriate since 2.49 also has two substituents on the α-position, which is known to make enones less reactive.
Chapter 2

Figure 2.12 Conformers of enones.

The extra conformational degrees of freedom in flexible enones such as 2.50 and chalcones (compared to 2-cyclohexenone) make them a problematic class of substrates to obtain high enantioselectivity as can also be seen from the result presented in the previous section. Additionally, complexation of a Lewis acid to the carbonyl functionality can occur in either a syn or anti fashion. The influences of these conformational effects on the enantioselectivity were studied in some detail by Woodward et al.\textsuperscript{51a}

So far, no working model has been developed to explain the high enantioselectivities obtained with some of the ligands mentioned in Sections 2.2.1 to 2.2.6. Possibly, molecular modeling using X-ray structures of chiral copper complexes (see Figure 1.5) as the starting point could provide valuable information in this area.\textsuperscript{71}

2.4 Rh-catalyzed enantioselective 1,4-addition of organoboronic acids

Besides the enantioselective copper catalyzed 1,4-addition of organozinc reagents, by far the most successful approach to achieve highly enantioselective conjugate addition has been the rhodium catalyzed addition of aryl- and alkenylboronic acids to enones, as developed by Hayashi et al.\textsuperscript{72} Using 3 mol\% of a Rh source and 3 mol\% of BINAP, 97\% ee was obtained in the 1,4-addition of a phenyl group to 2-cyclohexenone (Scheme 2.10). The 1,4-addition to 2-cyclopentenone and 2-cycloheptenone proceeded with 96\% and 93\% ee, respectively. Furthermore, linear enones also gave good results with ee’s of over 90\% and a variety of alkenyl boronic acids could also be used as nucleophiles with high enantioselectivity (>90\%). Recently, the successful 1,4-addition of boronic acids to a variety of substrates, such as α,β-unsaturated esters and lactones, 1-alkenylphosphonates and nitroolefins has been reported with ee’s ranging from 84\% to 98\%.\textsuperscript{73} Since these initial reports others have also applied the rhodium catalyzed 1,4-addition of organoboronic acids.\textsuperscript{74}

Scheme 2.10 Rhodium catalyzed enantioselective 1,4-addition of phenylboronic acid.
Advantages of this catalytic system are the stability of the organoboronic acids, allowing the use of protic solvents and water, and the fact that organoboronic acids in the absence of a rhodium catalyst are far less reactive towards enones than most other organometallic reagents and no 1,2-addition takes place. Since aryl- and vinyl-organozinc reagents do not perform well in the copper catalyzed 1,4-addition, the ‘Hayashi method’ is fully complementary to the copper catalyzed 1,4-addition of organozinc reagents.

2.5 Summary

In conclusion, since the first examples of highly enantioselective 1,4-additions using Cu(OTf)$_2$ and (S,R,R)-L$_1$, a wide variety of different ligands has been developed to catalyze the 1,4-addition of organozinc reagents to enones. Phosphoramidite (S,R,R)-L$_1$ remains one of the best ligands for cyclic substrates (see also next chapter) with >98% ee in the 1,4-addition to 2-cyclohexenone, although low ee’s were obtained for 2-cyclopentenone. High ee’s with this notoriously difficult substrate were obtained using phosphites (R,S)-2.20c (94% ee) and (S,S)-2.23 (89%) and phosphoramidite (S,S)-2.25 (83% ee). For acyclic substrates such as chalcone by far the best ligand is phoshpine (S)-2.34b, giving up to 98% ee. Very versatile is phoshpine ligand (S,S)-2.37, giving ee’s of 98% or higher with 2-cyclopentenone, 2-cyclohexenone, and 2-cycloheptenone. Because of the modularity of these ligands, they also have good potential in the 1,4-addition to other substrates and in catalyzing other reactions. The scope of substrates has also been extended and nitroolefins, α,β-unsaturated lactones, cyclopenten-3,5-dione monoacetals and cyclohexadienones can now be used without problems. For the introduction of aryl or vinyl groups, the Rh-BINAP catalyzed 1,4-addition of organoboronic acids is the method of choice, with high enantioselectivities being obtained on a variety of substrates.

2.6 References and notes

3 TADDOL = α,α’,α’-tetraphenyl-2,2’-dimethyl-1,3-dioxolane-4,5-dimethanol.


The catalytic enantioselective 1,4-addition of organometallic reagents

36 A. Martorell, R. Naasz, unpublished results.


69 This reduction might be achieved by Et₂Zn or by another reducing agent, see also ref. 26.


71 Apart from the X-ray structure shown in Figure 1.5 in Chapter 1, the only X-ray structure of a copper complex with one of the ligands discussed in section 2.2 was reported by Chan et al.; a [Cu(S,S)-2.23(MeCN)₂OTf] complex. See ref 26.


75 For the nickel catalyzed enantioselective 1,4-addition of vinylic zinc reagents prepared *in situ* from Me₂Zn and alkynes with ee’s up to 81%, see: S.-I. Ikeda, D.-M. Cui, Y. Sato, *J. Am. Chem. Soc.* 1999, 121, 4712.