Synthetic applications of the catalytic asymmetric 1,4-addition
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1.1 Chirality

The phenomenon known as chirality or handedness (Greek; cheir = hand) has fascinated chemists for more than a century. In 1874, Van ‘t Hoff proposed that the four substituents around a central carbon are placed at the corners of a regular tetrahedron (Figure 1.1, left). Consequently, when the four substituents on the central carbon atom are not identical, two different tetrahedral arrangements of the substituents are possible. These two different configurations, depicted as A and B, are mirror images and are called enantiomers (Figure 1.1, right). Enantiomers are chiral, that is to say they have handedness, and are not superimpossable.

Figure 1.1 Tetrahedral molecular models build by Van ‘t Hoff as displayed in the Boerhaave Museum in Leiden (left) and a schematic representation of two enantiomers (right).

The well established phenomenon that the two enantiomers of the same compound often have a completely different effect when applied as a drug, an agrochemical, or otherwise, emphasizes the need of obtaining chiral compounds in enantiomerically pure form. Several of the known methods to achieve this goal are summarized in Figure 1.2. The three basic strategies are making use of the chiral pool, separation of racemic materials, or asymmetric synthesis starting from prochiral substrates. The two routes that are the subject of this thesis, namely asymmetric catalysis and kinetic resolution, are given in bold in Figure 1.2.
Chapter 1

Racemates Prochiral substrates

Enantiomerically pure compounds

synthesis

resolution

kinetic enzymatic chemical
crystallization

diastereomers enantiomers

asymmetric synthesis
catalysis biocatalysis

Figure 1.2 Routes to enantiomerically pure compounds.

The term ‘chiral pool’ refers to the enantiomerically pure compounds that are found in nature. Upon isolation, these materials can be used as starting points for the synthesis of more elaborate enantiomerically pure compounds. The most widely used method for obtaining enantiomerically pure compounds for industrial applications is based on the separation of enantiomers by crystallization of a racemic mixture, i.e. a 1:1 mixture of the two enantiomers. Separation is usually achieved through crystallization of diastereomers formed by derivatization of the mixture of enantiomers with a single enantiomer of another compound. Other ways of carrying out such a separation are kinetic resolutions using either an enzyme or a chemical catalyst. A more detailed introduction to kinetic resolutions will be found in Chapter 7 of this thesis. Recently, separation of racemates through preparative HPLC or by the use of membranes has also become possible. Starting from prochiral compounds, enantiomerically pure compounds have been obtained by asymmetric synthesis using chiral auxiliaries (Section 1.2.2) or, alternatively, by employing either biocatalysis or catalysis using a chemical catalyst. Of the methods discussed above, asymmetric (bio)catalysis (the main subject of this thesis) is arguably the most elegant procedure, since it allows the formation of large quantities of enantiomerically pure products with the use of only small amounts of a chiral catalyst.

Asymmetric catalysis remains one of the most intriguing topics in organic chemistry, as is illustrated by the fact that the Nobel price for chemistry 2001 was awarded to W. S. Knowles, R. Noyori, and K. B. Sharpless for their pioneering work in the development of catalytic asymmetric hydrogenation and oxidation reactions. In the next paragraph the concept of asymmetric catalysis will be illustrated using some selected examples of the work of the Laureates of 2001.

In his groundbreaking work on catalytic enantioselective hydrogenations, Knowles made use of a combination of the development of the well known Wilkinson catalyst [(PPh3)3RhCl] (a soluble hydrogenation catalyst for unhindered olefins) and the discovery of methods to prepare optically active phosphines. By replacing the achiral triphenylphosphines in the Wilkinson catalyst with a chiral, optically active phosphine (1.3), the hydrogenation of α-phenylacrylic acid (1.1) was achieved with an enantiomeric excess...
(ee) of 15%. Although the enantioselectivity was only moderate, this result demonstrated that catalytic enantioselective hydrogenation was possible. This result eventually led to the highly successful variations of this reaction known today (vide infra).

Knowles himself, with his co-workers at Monsanto, exploited this initial result to develop a new synthesis of L-DOPA, also known as levodopa, a compound used in the treatment of Parkinson’s disease. With the use of the bidentate phosphine \((R,R)\)-DiPAMP, enamide 1.4 was hydrogenated to the protected amino acid 1.5, that can be converted to L-DOPA (1.6) by acid catalyzed hydrolysis (Scheme 1.2). This reaction, the so-called “Monsanto Process”, has been in operation since 1974, making it the first commercialized catalytic asymmetric synthesis using a chiral transition metal complex.

In 1980, Noyori and Takaya discovered BINAP (see Scheme 1.3), a new chiral diphosphine that turned out to be an extremely versatile ligand for various enantioselective catalytic processes. One example is the hydrogenation of 1.7 with the use of no more than 0.5 mol% of a \((S)\)-BINAP-Ru(OAc)₂ complex, to give the anti-inflammatory agent \((S)\)-naproxen (1.8) in 92% yield with 97% ee (Scheme 1.3). Further research revealed that functionalized ketones were also reduced with the use of BINAP-ruthenium complexes that contain halides. Some remarkable effects were found, e.g. the addition of a small amount of a diamine completely

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\text{HOOC} \quad \text{Ph} \quad \text{Rh-catalyst, } \text{H}_2 \quad \text{HOOC} \quad \text{Ph}
\]

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1.1 \quad \text{Pr} \quad \text{Me} \quad 1.2 \quad 15\% \text{ ee}
\]

\[
\text{HOOC} \quad \text{Ph} \quad \text{Rh-catalyst, } \text{H}_2 \quad \text{HOOC} \quad \text{Ph}
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1.1 \quad \text{Pr} \quad \text{Me} \quad 1.3 \ (69\% \text{ ee})
\]

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\text{1.3 (69% ee)}
\]

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\text{1.1} \quad \text{Rh-catalyst, } \text{H}_2 \quad \text{1.2}
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\text{1.1} \quad \text{Pr} \quad \text{Me} \quad 1.2 \quad 15\% \text{ ee}
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\text{HOOC} \quad \text{Ph} \quad \text{Rh-catalyst, } \text{H}_2 \quad \text{HOOC} \quad \text{Ph}
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\text{1.3 (69% ee)}
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\text{1.1} \quad \text{Rh-catalyst, } \text{H}_2 \quad \text{1.2}
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\text{1.1} \quad \text{Pr} \quad \text{Me} \quad 1.2 \quad 15\% \text{ ee}
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changed the chemoselectivity from reduction of a C\(=\)C double bond to reduction of a carbonyl group. The reduction was achieved with turnover numbers of almost 100,000. Even the use of racemic BINAP in the presence of catalytic amounts of an optically active and cheap chiral diamine was found to give high enantioselectivity in the reduction of ketones. The development of these highly chemo- and enantioselective carbonyl reductions has been described in detail by Noyori in a recent review.\(^\text{14}\)

\[
\begin{align*}
\text{MeO} & \quad \text{COOH} \\
\text{MeO} & \quad \text{COOH} \\
\text{PPh}_2 & \quad \text{PPh}_2 \\
\text{(S)} & \quad \text{(S)}-\text{BINAP} \\
\text{MeOH, H}_2 & \quad \text{MeOH, H}_2 \\
\end{align*}
\]

\[
\text{Scheme 1.3 Catalytic asymmetric synthesis of (S)-naproxen (1.8) using a (S)-BINAP-Ru complex.}
\]

In 1980 Sharpless and Katsuki discovered a highly enantioselective epoxidation reaction, using titanium(IV)tetraisopropoxide, \(t\)-butyl hydroperoxide, and enantiomerically pure dialkyl tartrate.\(^\text{15}\) Although stoichiometric amounts of Ti and tartrate were needed initially, the reaction was made catalytic (5 to 10 mol\% of catalyst) by the addition of molecular sieves to remove traces of water from the reaction mixture.\(^\text{16}\) An illustrative example of the power of this reaction is the chemoselective and enantioselective epoxidation of geraniol (1.9), using only catalytic amounts of \(\text{Ti(Oi-Pr)}_4\) and \((R,R)\)-diethyltartrate 1.11 (Scheme 1.4). Due to coordination of the hydroxy group of geraniol to the titanium complex the epoxidation occurs selectively at the allylic double bond. Due to the generality, practicality, and reproducibility the Sharpless epoxidation is used nowadays in ton-scale industrial processes in the pharmaceutical industry.\(^\text{17}\)

\[
\begin{align*}
\text{Ti(Oi-Pr)}_4 & \quad \text{EtOOCCOOEt} \\
4 \text{Å mol sieves, } -20\ ^\circ\text{C} & \quad \text{99\% yield} \\
\end{align*}
\]

\[
\text{Scheme 1.4 Chemo- and enantioselective Sharpless epoxidation of geraniol (1.9).}
\]

The aforementioned catalytic enantioselective reactions are only a few examples of enantioselective reactions that have been developed over the last decades. The interested reader is referred to several excellent papers on this topic.\(^\text{18}\)
1.2 Stereoselectivity in C-C bond formation through 1,4-additions

The 1,4-addition of carbon nucleophiles to α,β-unsaturated compounds is one of the most important methods for the formation of carbon-carbon bonds in organic chemistry.\textsuperscript{19} Especially the wide variety of donors and acceptors that can be used in this reaction makes it a highly versatile tool, for example in the synthesis of biologically active compounds such as prostaglandins.\textsuperscript{20} The following overview is by no means intended to exhausting. Again the interested reader is referred to review papers written on this topic.\textsuperscript{21}

1.2.1 Regioselectivity

The nucleophilic 1,4-addition is an interesting reaction from the viewpoint of selectivity. First of all there is the problem of competition between 1,4-addition and 1,2-addition reactions (Scheme 1.5). The selectivity between 1,2- and 1,4-addition is influenced by several parameters, but in general the use of soft nucleophiles such as cuprates will result in high selectivities for the 1,4-addition product and hard nucleophiles (Grignard and lithium reagents) will result in formation of the 1,2-addition product.

\[
\begin{align*}
R^1\shortparallel\text{\textit{unsaturated}} & \quad \text{1,2-addition} \quad R^1\shortparallel\text{\textit{unsaturated}} \\
R^1\shortparallel\text{\textit{unsaturated}} & \quad \text{1,4-addition} \quad R^1\shortparallel\text{\textit{unsaturated}}
\end{align*}
\]

\textbf{Scheme 1.5} 1,2-Addition vs. 1,4-addition.

1.2.2 Diastereoselective 1,4-additions using either chiral acceptors or chiral nucleophiles

Due to the importance of the 1,4-addition of cuprates as a synthetic tool, it is not surprising that attempts to achieve an asymmetric version of this reaction were made at a very early stage in organocopper chemistry. The most straightforward method to perform asymmetric 1,4-additions is the use of a chiral auxiliary that is covalently linked to either the α,β-unsaturated substrate or to the organocopper reagent. After the diastereoselective 1,4-addition, removal of the chiral auxiliary results in an overall enantioselective transformation.

The use of covalently linked chiral auxiliaries for α,β-unsaturated compounds has been the subject of extensive research.\textsuperscript{21,22} One successful example of this approach was published by Helmchen and Wegner in 1985 (Scheme 1.6).\textsuperscript{23}
These authors used a chiral hydroxysulfonamide auxiliary that after esterification with an \( \alpha,\beta \)-unsaturated acid was able to shield one of the enantiotopic faces of ester 1.12. This led to very high diastereoselectivities (>99:1 diastereomeric ratio for several examples with different \( R_1 \) and \( R_2 \)) in the 1,4-addition products using both lithium and Grignard based cuprates. Removal of the auxiliary under mild conditions allowed isolation of the enantiomerically pure acids 1.14 and the chiral auxiliary (> 90% recovered).

The alternative, the use of chiral copper reagents, has been studied less extensively. An illustrative example of this approach with the chiral cuprate 1.16 (derived from imine 1.15) was reported by Yamamoto et al.\textsuperscript{24} Diastereoselective addition of cuprate 1.16 to 2-cyclopentenone followed by hydrolysis of the imine upon workup yields 3-substituted cyclopentanone 1.17 with 78% ee (Scheme 1.7).

Although high enantioselectivities have been obtained with the chiral auxiliary approach, the inherent disadvantages are obvious. First of all, stoichiometric amounts of the often expensive chiral auxiliary are needed. Furthermore, two extra steps, attachment and removal of the auxiliary, are required to perform the overall enantioselective 1,4-addition. Therefore, a major challenge has been the development of enantioselective 1,4-additions of organometallic reagents in the presence of only catalytic amounts of chiral ligands and transition metals.
1.2.3 **Catalytic enantioselective 1,4-additions**

The development of catalytic enantioselective 1,4-additions started with the use of stoichiometric or substoichiometric amounts of heterocuprates containing chiral alcohols, amines, or thiols as non-transferable ligands. A notable example of this approach is the synthesis of (R)-(−)-muscone (1.19) in 99% ee using substoichiometric amounts of ligand and copper as published by Tanaka *et al.* (Scheme 1.8).25

![Scheme 1.8 Synthesis of (R)-muscone (1.19).](image-url)

The pioneering work of Lippard *et al.* 26 led to the development of the first truly catalytic enantioselective 1,4-addition. Although the initial enantioselectivities with the copper complex based on aminotropone imine 1.22 were low (4-14% ee), this problem was overcome by the addition of HMPA and Ph$_2$(t-Bu)SiCl. 27 An ee of 74% was obtained in the 1,4-addition of $n$-BuMgCl to 2-cyclohexenone with 5 mol% of the copper catalyst that was generated from (S,S)-1.22, CuBr•SMe$_2$, and $n$-BuLi (Scheme 1.9).

![Scheme 1.9 First catalytic enantioselective 1,4-addition of Grignard reagents to 2-cyclohexenone.](image-url)

The results obtained by Lippard *et al.* inspired further research and led to the development of a variety of catalysts for this reaction that did not need the addition of large amounts of additives such as HMPA and trialkylsilyl chlorides and that gave ee’s up to 92% in the 1,4-addition to 2-cyclohexenone (Figure 1.3). 2$d,e,28$
Shortly after Lippard published his work on the enantioselective 1,4-addition of Grignard reagents, Soai discovered the first enantioselective nickel catalyzed 1,4-addition of organozinc reagents,\textsuperscript{29} based on earlier work by Green \textit{et al.}\textsuperscript{30} The use of organozinc reagents has some distinct advantages over the use of other organometallic reagents. They are less basic and are tolerant to a variety of functional groups, present in either the reagent itself or in the substrate. Another advantage is that organozinc reagents react extremely sluggishly with carbonyl groups, but catalysis can be achieved by the use of either activating ligands or transmetallation (Scheme 1.10, I and II, respectively).

\textbf{Scheme 1.10 Activation of organozinc reagents.}
The activating effect of (chiral) ligands has been explained by changes in geometry and bond energy of the organozinc reagent. For instance, dimethylzinc has a linear structure and is not reactive towards aldehydes and ketones, but upon coordination of triazine, a tetrahedral structure is produced and the zinc-carbon bond is slightly elongated (Scheme 1.10, I). This results in enhanced reactivity of the dialkylzinc reagent, a feature extensively used in the catalytic enantioselective 1,2-addition. Alternatively, organozinc reagents can be converted into more reactive organometallic species by transmetallation, as has been demonstrated for Ni, Cu, Pd, Ti and Co.

Since the initial results obtained by Soai et al. (vide supra), the nickel catalyzed enantioselective 1,4-addition has thoroughly been investigated in our research group and by others and has led to the development of a variety of successful chiral ligands, such as aminoalcohols, pyridine alcohols, diamines, aminoamides, thiols, and oxazolines. With these ligands ee’s up to 95% have been reached. Similar reactions were successfully performed also with cobalt salts instead of nickel. A recent example of a successful Ni-catalyzed enantioselective 1,4-addition, using a new type of aminoalcohol, was published by Nayak et al. (Scheme 1.11). With the use of 9 mol% of Ni(acac)2 and 10 mol% of (S)-1.29 ee’s ranging from 12-93% were reached. The best result was obtained with methoxy-substituted chalcone 1.30 as the substrate.

Scheme 1.11 Ni-catalyzed enantioselective 1,4-addition using to chalcone 1.30 using (S)-1.29.

Although excellent results have been obtained in the nickel catalyzed enantioselective 1,4-addition, complete enantioselectivity was not achieved. Also the reactions are generally very substrate specific. Especially cyclic enones did not give satisfactory results with ee’s generally not exceeding the 10% level. Due to the affinity of chiral Ni-complexes for the carbonyl oxygen, highly enantioselective alkyl transfer only occurs in the case of s-cis enones as shown in Figure 1.4 (intermediate A). Intermediate B probably is formed in the case of 2-cyclohexenone (s-trans enone) where the chiral Ni-complex is too distant from the β-position thereby decreasing the stereocontrol in the conjugate addition step. Note that enantioselective copper catalyzed 1,4-additions should be possible to both s-cis- and s-trans enones, since copper complexes probably coordinate to the double bond of the enone (C) (See also Section 2.3 in Chapter 2).
1.3 Copper catalyzed 1,4-additions of organozinc reagents

In 1993 Alexakis et al. published the first example of a copper catalyzed enantioselective 1,4-addition of Et₂Zn to 2-cyclohexenone for which they used ephedrine based phosphorus ligand 1.32 (Scheme 1.12), previously investigated by the same group in the enantioselective copper catalyzed 1,4-addition of Grignard and organolithium reagents. Although the enanioselectivity of the reaction with 2-cyclohexenone was only moderate (32% ee) and only racemic material was obtained in the 1,4-addition to chalcone, these initial results inspired further research into the enantioselective copper catalyzed 1,4-addition of organozinc reagents. In our group, André de Vries investigated the use of bis-β-naphthol (BINOL) based phosphoramidite (S)-1.34a, a new type of ligand previously synthesized by Ron Hulst. With the use of a chiral copper catalyst prepared in situ from CuI and (S)-1.34a, 35% ee was obtained for the 1,4-addition to 2-cyclohexenone (1.20) and 49% ee for chalcone (1.35) (Scheme 1.13). Although the obtained enantioselectivities were only moderate, this was one of the first examples of a catalytic system that performed well for both cyclic and acyclic enones. Further modification of the ligand, especially of the (achiral) amine part, led to a variety of phosphoramidites of which (S)-1.34b, with two bulky isopropyl substituents...
on the nitrogen, turned out to be the best. The copper source also was changed to Cu(OTf)$_2$ (Tf = SO$_2$CF$_3$), which was found to be the best copper salt, probably due to superior solubility and the absence of a strongly coordinating anion.$^{46,48}$

![Scheme 1.13 Copper-phosphoramidite catalyzed 1,4-addition to cyclohexenone and chalcone.](image)

With the use of this Cu(OTf)$_2$-$(S)$-$\text{1.34b}$ catalyst, 60% ee was obtained in the 1,4-addition of Et$_2$Zn to 2-cyclohexenone and 90% ee for chalcone.$^{46}$ Also, these phosphoramidite based catalysts displayed high activity with full conversion being reached within 3 h and excellent chemo- and regioselectivities (>95% for 1,4-addition). Furthermore, the use of functionalized organozinc reagents containing an ester moiety proved to be possible without loss of enantioselectivity compared to Et$_2$Zn.
André de Vries was also able to obtain crystals of a CuI-(S)-1.34a complex that were suitable for X-ray analysis (Figure 1.5). Three ligands are coordinated to the central copper ion, creating a C3-symmetrical complex. Although this structure is probably not the catalytically active species, a study of this X-ray structure indicated that further modification of the amine part, introducing an additional chiral moiety, might influence the chiral environment of the catalyst and thus the enantioselectivity in the 1,4-addition.

With this in mind, Leggy Arnold of our group synthesized phosphoramidite ligand (S,R,R)-L1, starting from (S)-BINOL (1.35) and using commercially available C2-symmetric amine 1.37 (Scheme 1.14). Initially only moderate yields of ~40% were obtained, mainly due to loss of product during column chromatography. Recrystallization of the crude product from acetone, however, allowed the isolation of (S,R,R)-L1 in ~70% yield as well as larger scale preparations.

With the catalyst prepared from Cu(OTf)2 (2 mol%) and (S,R,R)-L1 (4 mol%), (S)-1.33 was obtained by the 1,4-addition of Et2Zn to 2-cyclohexenone (1.20) in 94% yield and >98% ee. This represents the first example of essentially complete enantioselection in a catalytic asymmetric 1,4-addition (Scheme 1.15).

With the other diastereomer of L1, prepared from (S)-BINOL and amine (S,S)-1.37, (S)-1.33 was obtained with 91% ee, showing a modest matched-mismatched effect between the two diastereomers. This result also indicates that the stereochemical outcome of the reaction is dictated by the absolute stereochemistry of the BINOL moiety in the phosphoramidite ligand.
Figure 1.6 Substrates and the ee's obtained in the enantioselective 1,4-addition of Et₂Zn using (S,R,R)-L1 under the standard conditions (see Scheme 1.15).

The 1,4-addition to cyclohexenones with two substituents on the 4-position, e.g. 1.38 and 1.39, also turned out to be highly enantioselective in the presence of Cu(OTf)_2 and (S,R,R)-L1, giving >98% ee (Figure 1.6). The synthetically interesting monoprotected dienone substrate 1.40 also gave a satisfactory ee of 97%. The 1,4-addition to 2-cyclopentenone (1.41) proceeded with very low enantioselectivity (~10%) and in this case (S,S,S)-L1 gave a better result (30% ee). The 1,4-addition of Et₂Zn to chalcone (1.35) proceeded with 75% ee, showing that (S,R,R)-L1 is not the best ligand for acyclic enones (see Scheme 1.13). Reactions using different organozinc reagents such as Me₂Zn, i-Pr₂Zn, and functionalized organozinc reagents gave satisfactory also, ee’s ranging from 94 to 98%, which demonstrated the versatility of the catalytic system.

The enantioselective 1,4-addition is attractive also from a synthetic point of view because the enolates formed in this reaction can be trapped by a variety of electrophiles. The zinc enolates formed in the enantioselective 1,4-addition, e.g. 1.42, have been quenched by various aldehydes to give enantiomerically enriched aldol products (Scheme 1.16). Apart from Et₂Zn and benzaldehyde, this reaction gave good results also with the use of Me₂Zn and various aldehydes with ee’s ranging from 91-97%.

Scheme 1.16 Enantioselective 1,4-addition and subsequent aldol reaction.
Chapter 1

1.4 Aims and outline of this thesis

The discovery of the first catalytic enantioselective 1,4-addition that yields products that are virtually enantiomerically pure (>98% ee) has been described in the previous section. The value of catalytic enantioselective processes is largely determined by their applicability in synthetic organic chemistry (see Section 1.1). In this context, the main goal of the research described in this thesis was to develop synthetic applications for enantioselective copper-phosphoramidite catalyzed 1,4-additions. In Chapter 2, a concise review is presented of the explosion of papers on different catalytic systems and applications for the enantioselective 1,4-addition that appeared since the work described in this thesis started in 1997. Chapter 3 deals with the successful enantioselective 1,4-addition on various substrates, especially 7- and 8-membered cycloalkenones. The efficiency of the copper-phosphoramidite catalyst is also discussed in this chapter. In Chapter 4, two different methodologies for the synthesis of enantiomERICALLY enriched bicyclic products are presented, based on the enantioselective 1,4-addition. In both cases the ring closure is effected by an aldol condensation. The first method is based on the use of acetal functionalized organozinc reagents and the second on a tandem copper catalyzed 1,4-addition-palladium catalyzed allylic substitution reaction. In Chapter 5 attempts are described towards the catalytic enantioselective synthesis of a steroid skeleton by the use of functionalized organozinc reagents in the tandem 1,4-addition-allylic substitution. Although we did not complete the synthesis of the steroid skeleton, the preliminary results indicate that the synthesis of, for instance, estron, ought to be possible. Chapter 6 again deals with the synthesis of bicyclic products. The methodology is based on a combination of the enantioselective 1,4-addition and ring closing metathesis, thus providing a route to different bicyclic products in which the size of both rings can easily be varied independently of one another. Chapter 7 describes the application of the copper-phosphoramidite catalyst in the kinetic resolution of substituted 2-cyclohexenones with very high selectivities. The multigram scale on which these resolutions have been performed makes it a valuable method for obtaining these enantiomerically pure building blocks.

1.5 References and notes

3 Diastereomers are stereoisomers that are not related as mirror images and usually have different physical properties.
A molecule is said to be prochiral when addition to a double bond or replacement of one of two equivalent groups at a particular atom leads to the creation of a new chiral centre, see ref. 2.


See chapter 18 of ref. 4a.


22 For a short overview see chapter 8 of ref. 19b.


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40 a) A. H. M. de Vries, B. L. Feringa, Tetrahedron: Asymmetry 1997, 8, 1377.


It should be noted that the complex shown in Figure 1.5 gave similar results in the enantioselective 1,4-addition to 2-cyclohexenone compared to the catalyst prepared in situ from CuI and (S)-1.34a. See chapter 6 of ref. 42.

L. A. Arnold, High Enantioselective Copper Catalysed Conjugate Addition of Diorganozincs to Cyclic and Acyclic Enones, undergraduate research report, Groningen, 1997.


The ee of (S)-1.33 using (S,S,S)-L1 as the ligand was previously incorrectly reported to be 75%, see ref. 52.


See chapter 9 of ref. 19b.