Synthetic applications of the catalytic asymmetric 1,4-addition
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Chapter 7

Copper-phosphoramidite catalyzed kinetic resolution of chiral 2-cyclohexenones

7.1 Chiral cyclohexenones

Chiral non-racemic 2-cyclohexenones are attractive building blocks for the synthesis of a variety of natural products. A limited number of naturally occurring optically active cyclohexenones, such as pulegone (7.1), carvone (7.2) and piperitone (7.3), can be obtained from the so-called “chiral pool” (see Chapter 1) and are widely used in natural product synthesis (Figure 7.1). Advantages of these compounds are that they are cheap and readily available in large quantities. The main drawbacks are: (i) the advantages mentioned above only pertain to the naturally occurring enantiomer and (ii) the lack of structural diversity in these naturally occurring compounds.

![Figure 7.1 Optically active cyclohexenones from the chiral pool.]

Because of this lack of structural diversity in the chiral pool there is much interest in the development of routes to non-natural enantiomerically pure cyclohexenones. Until recently, the most common method to obtain such non-natural cyclohexenones was the derivatization of cyclohexenones from the chiral pool. For instance, the important synthons 4-methyl-2-cyclohexenone (7.4) and 5-methyl-2-cyclohexenone (7.5) can both be obtained enantiomerically pure from (R)-7.1 and (R)-7.2. The main disadvantages of these methods are that they consist of multistep syntheses (3 steps or more) with overall yields that are generally quite low and again that only one of the enantiomers is readily available. Both 7.4 and 7.5 have been used in the synthesis of various natural products, two examples of which are depicted in Scheme 7.1.
**Scheme 7.1** Examples of natural products prepared from enantiomerically pure cyclohexenones.

The groups of Corey and Sato recently introduced elegant methods for the synthesis of enantiomerically pure 5-substituted-2-cyclohexenone synthons 7.6 and 7.7, respectively. Starting from anisole, each of the enantiomers of 5-trimethylsilyl-2-cyclohexenone (7.6) can be obtained in 6 steps. The key step is the highly efficient enzymatic kinetic resolution of alcohol 7.8 by Lipase PS yielding both the alcohol and acetate 7.9 with ee >99% (Scheme 7.2a). Enantiomerically pure 5-(t-butyldimethylsiloxy)-2-cyclohexenone (7.7) has been obtained by Sato et al. from commercially available 7.10 in a multistep synthesis (Scheme 7.2b).

**Scheme 7.2** Synthesis of 2-cyclohexenone synthons as reported by Corey (a) and Sato (b).
Both of these synthons can be used to prepare a variety of other 5-substituted cyclohexenones in high enantiomeric purity, using a two step procedure as is illustrated for 7.7 in Scheme 7.3. Addition of the higher order cuprate \( n\text{-Bu}_2\text{Cu(CN)Li}_2 \) leads selectively to the \( \text{trans-3,5-disubstituted cyclohexanone} \ 7.11\), which is followed by elimination of the silyloxy group under mild conditions with DBU in DMF at 20 °C. An elegant feature of this procedure is that the use of lower order cuprates like \( n\text{-BuCu(CN)Li} \) results in a high selectivity for the \( \text{cis} \) compound, enabling the preparation of both enantiomers of 7.12 starting from a single enantiomer of 7.7. This remarkable result can be explained by the ability of the oxygen of the silyloxy group to coordinate to copper in lower order cuprates leading to \( \text{cis} \) addition (Scheme 7.3).

Other, less general, methods for the synthesis of enantiomerically pure 2-cyclohexenones, have also been reported. One method by Taber et al.\textsuperscript{9} starts from readily available optically active alkenyl cyclopropanes. Irradiation of these cyclopropanes with UV light in the presence of Fe(CO)\textsubscript{5} results in a ring expansion giving 5-substituted cyclohexenones with up to 95% ee. Meyers \textit{et al.}\textsuperscript{10} used chiral bicyclic lactams as homoenolate equivalents which can be alkylated stereoselectively after which the products can be converted into optically active 5-alkyl-2-cyclohexenones in two steps. The catalytic deracemization of allylic esters or carbonates can also lead to precursors for 5-substituted cyclohexenones, as has been reported by Trost \textit{et al.}\textsuperscript{11}

### Scheme 7.3

\( \text{Synthesis of both enantiomers of 7.12 from a single enantiomer of 7.7.} \)

#### 7.2 Kinetic resolution

Although numerous methods are known for the synthesis of enantiomerically enriched cyclohexenones, the major drawback is that they all consist of rather lengthy procedures. On the other hand, various racemic 2-cyclohexenones are readily accessible (\textit{vide infra}). This
inspired us to develop a general method to obtain optically active 2-cyclohexenones by kinetic resolution of racemic 2-cyclohexenones, based on the copper-phosphoramidite catalyzed 1,4-addition to enones.

Although enzyme catalyzed kinetic resolutions have been known for a long time, the use of chemical catalysts to perform kinetic resolutions is a relatively new research topic. The first example of a successful kinetic resolution using a chemical catalyst, although in stoichiometric amounts, was published in 1981 by Sharpless and co-workers.13 Their previously reported procedure, for the catalytic asymmetric epoxidation of allylic alcohols was adapted to the kinetic resolution of chiral allylic alcohols. A typical example is given in Scheme 7.4; using 1.2 equivalents of (+)-diisopropyl tartrate (DIPT), 1 equivalent of Ti(Oi-Pr)₄ and 0.6 equivalent of t-butyl hydroperoxide (TBHP), (S)-7.13 was selectively epoxidized to give 7.14 and (R)-7.13 was recovered with >96% ee. In 1986, a catalytic version of this resolution was reported, using only 5 to 10 mol% of catalyst.15

\[
\text{OH OH OH O(+)-DIPT (1.2 equiv)} \\
\text{Ti(Oi-Pr)₄ (1.0 equiv)} \\
\text{TBHP (0.6 equiv)} \\
\text{[7.13] threo/erythro: 97/3} \\
\text{(R)-7.13 >96% ee} \\
\text{7.14}
\]

\text{Scheme 7.4 Kinetic resolution of allylic alcohols as reported by Sharpless et al.13}

Since this important contribution, different procedures for kinetic resolutions using chemical catalysts have been developed.16 A recent and very elegant example is the selective acetylation of alcohols, using planar-chiral DMAP derivative 7.15 as the catalyst, developed by Fu et al. (Scheme 7.5).17

\[
\text{OH} \\
\text{[7.16] Ph} \\
\text{[7.15] Et₂N, Ac₂O, 0 °C} \\
\text{1-2.5 mol%} \\
\text{[Ph]-7.16 98% ee, 53% conv.} \\
\text{[Ac]-7.17}
\]

\text{Scheme 7.5 Kinetic resolution of allylic alcohols by selective acylation.
7.2.1 Theory of kinetic resolution

As briefly mentioned in Chapter 1, a kinetic resolution can be defined as a process in which one of the enantiomers of a racemic mixture is more readily transformed into a product than the other (Scheme 7.6).\(^{18}\)

\[
\begin{align*}
S_S & \xrightarrow{k_S} P \\
S_R & \xrightarrow{k_R} Q
\end{align*}
\]

Scheme 7.6 Kinetic resolution.

If \(k_S \neq k_R\) (e.g., \(k_S > k_R\)) and the reaction is stopped before completion, the starting material will be enriched in the \(R\) enantiomer. In the ideal case, where \(k_S \gg k_R\), only the \(S\) enantiomer reacts so that at 50% conversion a mixture of 50% of the \(R\) enantiomer of the starting material and 50% product \(P\) is obtained. Note that the products \(P\) and \(Q\) can be achiral (identical or not) or chiral, and that the nature of the products is irrelevant if one is only interested in the ee of the remaining starting material. The difference in specific rate constants is caused by the fact that the reaction is mediated by a chiral catalyst, enzyme or chiral reagent. The relative rates of reaction for the substrate enantiomers, typically expressed as \(s\) (selectivity factor), \(E\) (for enzymatic processes), or \(k_{rel}\), are dictated by the magnitude of \(\Delta \Delta G^\ddagger\). This corresponds to the difference in energy between the diastereomeric transition states in the selectivity-determining step of the catalytic reaction.\(^{16}\) For processes that show first-order kinetics in substrate, \(s\) can be calculated using equation 1 where \(c\) (0 ≤ \(c\) ≤ 1) is the conversion and \(ee\) (0 ≤ \(ee\) ≤ 1) is the ee of the starting material.\(^{19}\)

\[
s = k_{rel} = k_{fast}/k_{slow} = \frac{\ln[(1-c)(1-ee)]}{\ln[(1-c)(1+ee)]} \quad \text{Eq. (1)}
\]

When studying a kinetic resolution by a chemical catalyst that displays the simplest form of Michaelis-Menten kinetics, i.e., reversible binding of both enantiomers of the substrate to the catalyst followed by an irreversible product forming step, the following general scheme applies (Scheme 7.7). From this simple scheme it becomes clear that the selectivity factor in kinetic resolutions depends on both the equilibrium binding (\(K_S\) vs. \(K_R\)) and the rate constants (\(k'_S\) vs. \(k'_R\)).

\[
\begin{align*}
S_S & \xrightarrow{K_S} S_S\text{-cat}^* \xrightarrow{k'_S} P_S \\
S_R & \xrightarrow{K_R} S_R\text{-cat}^* \xrightarrow{k'_R} P_R
\end{align*}
\]

Scheme 7.7 Kinetic resolution displaying simple Michaelis-Menten kinetics.
Two borderline cases can now be identified for a successful kinetic resolution; (i) $K_S \neq K_R$, e.g. $K_S \gg K_R$ and $k'_S \cong k'_R$. In this case kinetic resolution is accomplished because the $S$ enantiomer of the substrate binds more readily to the catalyst than the $R$. In the other borderline case; (ii) $K_S \equiv K_R$ and $k'_S \neq k'_R$, e.g. $k'_S \gg k'_R$, there is no preference for the formation of either of the substrate-catalyst complexes ($S_{S\text{-cat}}^*$ and $S_{R\text{-cat}}^*$) and the chiral discrimination is achieved by the large difference in rate in the product formation step. In practice these two factors can, of course, both play a role and the effects of equilibrium binding and rate constants can counteract or strengthen each other. A way to deconvolute these two factors by using enantiopure catalysts was recently reported by Blackmond.20

### 7.2.2 Kinetic resolution: practical considerations

One of the most attractive features of kinetic resolutions from a practical point of view is that even with a relatively low selectivity, unreacted substrate can be obtained with high ee simply by carrying the reaction to high enough conversion. As is shown in Figure 7.2,13,21 a selectivity factor of 10 theoretically suffices to obtain the substrate with an ee of 98% in 30% yield and a selectivity of 100 or higher gives >99% ee at conversions just over 50%.

![Figure 7.2](image)

**Figure 7.2** Ee of starting material vs. conversion for different $s$ values.

A second advantage is the fact that the remaining starting material can be obtained with absolute enantiomeric purity (99.9999…%), something not often accomplished with asymmetric catalysis or synthesis. In other words: “…the energy difference, manifested as a relative rate difference, represents a constant and unrelenting differential pressure upon the two enantiomers. This winnowing should continue until the last molecule of the more reactive enantiomer is swept away, and one is left with a substance possessed of absolute enantiomeric purity…” (Sharpless, 1981).13
In some cases parallel kinetic resolution (PKR) can be an improvement over the standard procedures. In a standard kinetic resolution build up of the less reactive enantiomer will cause the two enantiomers to react equally fast as the resolution reaches completion, due to the balance between the inherent rate and the available concentration. In a PKR, the build up of the less reactive enantiomer is prevented by converting it to a different product, either by the catalyst itself or by an achiral reagent, thus giving a higher ee in the product.\textsuperscript{22}

The major drawback of kinetic resolutions is that the maximum theoretical yield of enantiomerically pure recovered starting material is 50%. If the product is the desired compound, it is sometimes possible to racemize the starting material \textit{in situ}, allowing the isolation of enantiomerically pure product in 100% yield starting from racemic starting material. This process is known as dynamic kinetic resolution.\textsuperscript{23} In other cases it is possible to racemize the remaining enantiomer of the starting material after isolation. Regardless the fact that in most cases the maximum yield will be 50%, it is simplistic to consider kinetic resolutions as being inelegant or impractical, since racemates often are much less than half as expensive as their enantiomerically pure counterparts.\textsuperscript{16}

In conclusion, at least some of the following conditions proposed by Jacobsen,\textsuperscript{16} should be met for a kinetic resolution reaction to be of use in practical organic synthesis:

1. The racemate is cheap and/or readily available and no satisfactory enantioselective, chiral pool, or classical resolution route to the product exists.
2. The catalyst is highly selective for one enantiomer\textsuperscript{24} and is effective at low loadings.
3. The catalyst is inexpensive and/or it can be recycled efficiently.
4. The reaction is economical and safe: inexpensive stoichiometric reagents, no undue dangers associated with the reagents, high volumetric throughput, and a minimum of waste generated.
5. The resolved starting material and converted product are easily separated.
6. In the ideal case, both the product and resolved substrate are valuable and recoverable in highly enantioenriched form.

### 7.3 Kinetic resolution of 5-methyl-2-cyclohexenone (7.5)

#### 7.3.1 Kinetic resolution vs. 1,4-addition

We anticipated that the high enantioselectivity obtained by the copper-phosphoramidite catalysts in the enantioselective 1,4-addition of diethylzinc to 2-cyclohexenone, combined with the high \textit{trans}-diastereoselectivity generally found in the 1,4-addition to 5-substituted-2-cyclohexenones (\textit{e.g.} 7.5), should provide high selectivity in the resolution of such compounds (Scheme 7.8). When Lippard \textit{et al.} reported the first catalytic enantioselective 1,4-addition (see Chapter 1, Section 1.2.3), they already realized the potential of this reaction
in the kinetic resolution of racemic 2-cycloalkenones and performed some initial experiments to proof the principle, but only low selectivities were obtained.\footnote{25}

\[
\text{O} \quad \text{enantioselective} \quad \text{O}
\]
\[
\text{1,4-addition}
\]

\[
\text{O} \quad \text{kinetic} \quad \text{resolution}
\]
\[
\text{7.5}
\]

**Scheme 7.8** Enantioselective 1,4-addition and kinetic resolution.

This type of kinetic resolution would involve the creation of an additional stereogenic centre in a racemic mixture. The mathematical relationships between conversion, ee of starting material and diastereomeric excess and ee of the products for these kinds of systems have been developed by Kagan et al.\footnote{26} Throughout this chapter, the focus will lie on the synthetically interesting starting materials and not on the products. The trans-diastereoselectivity\footnote{27} in these 1,4-additions can be rationalized through unfavorable interactions between R and Me in the transition state that would lead to the cis product via intermediate 7.19, resulting in the predominant formation of the trans product, as demonstrated by Corey for the 1,4-addition of Me\textsubscript{2}CuLi to 5-substituted-2-cyclohexenones (Scheme 7.9).\footnote{28}

\[
\text{O}
\]
\[
\text{R}
\]
\[
\text{Me}_2\text{CuLi}
\]

\[
\text{Me}_2\text{CuLi}
\]

**Scheme 7.9** Favored and disfavored copper intermediates as proposed by Corey et al.\footnote{28}
7.3.2 *Kinetic resolution of 7.5: ligand variation*

After encouraging preliminary experiments we decided to check the viability of such an approach systematically and tested ligands L1-L6 in the kinetic resolution of rac-7.5 (Figure 7.3). Racemic 7.5 was synthesized in one step from the cheap starting materials ethyl acetoacetate and crotonaldehyde according to a literature procedure, although the obtained yields were much lower than those reported by the authors (~20%, lit. 78%, Scheme 7.10).²⁹

![Scheme 7.10 Synthesis of 5-methyl-2-cyclohexenone.](image)

The resolutions were all performed under conditions typical for the asymmetric 1,4-addition on a 1 mmol scale (Scheme 7.11). Samples were taken from the reaction mixture at certain intervals after which both conversion (relative to internal standard) and ee were determined in one run using a chiral GC column. From these data \( s \) was calculated using Eq. 1 (see Experimental Section for details).¹⁹,³⁰

![Figure 7.3 Ligands used for the kinetic resolution of 7.5.](image)
With the use of 1 mol% of Cu(OTf)$_2$, 2 mol% of (S,R,R)-L1 and 0.8 equivalents$^{31}$ of Et$_2$Zn in toluene at $-40\,^\circ\mathrm{C}$ for the resolution of racemic 7.5, an ee of 88% was reached for (R)-7.5 at 48% conversion, which indicated that $s = 120$ (Table 7.1). After 20 minutes 53% conversion was reached and unreacted 7.5 was found with an ee of 99%, demonstrating that the copper-phosphoramidite catalyst reacts almost exclusively with one of the enantiomers of 7.5. Comparison of the optical rotation of an isolated sample of the unreacted 7.5 with data reported in the literature,$^8a$ showed that the recovered 7.5 had the $R$ configuration.

\[ \text{rac-7.5} \xrightarrow{\text{Et}_2\text{Zn (0.8 equiv.)}} \left\{ \begin{array}{c} (R)\text{-7.5} \\ (S,S)\text{-7.20} \end{array} \right. \]

Scheme 7.11 Kinetic resolution of 7.5 under conditions typical for the asymmetric 1,4-addition.

This means that (S)-7.5 is converted by the chiral catalyst to the product faster than (R)-7.5, which we actually predicted beforehand on the basis of the preferred trans-addition (vide supra) and the fact that the 1,4-addition of Et$_2$Zn to 2-cyclohexenone in the presence of (S,R,R)-L1 produces (S)-3-ethylcyclohexanone (see also Scheme 7.8).$^{32}$ The results obtained with the other phosphoramidites are summarized in Table 7.1.

### Table 7.1 Kinetic resolution of 7.5 with Et$_2$Zn, Cu(OTf)$_2$ and ligands L1-L6.

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand</th>
<th>T ($^\circ\mathrm{C}$)</th>
<th>t (min)</th>
<th>convn. (%)</th>
<th>ee (%)</th>
<th>$s$</th>
<th>conf.$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(S,R,R)-L1</td>
<td>-40</td>
<td>15</td>
<td>48</td>
<td>88</td>
<td>120</td>
<td>R</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>(S,S,S)-L1</td>
<td>-30</td>
<td>15</td>
<td>42</td>
<td>62</td>
<td>24</td>
<td>R</td>
</tr>
<tr>
<td>3</td>
<td>(S,R)-L2</td>
<td>-30</td>
<td>90</td>
<td>49</td>
<td>86</td>
<td>50</td>
<td>R</td>
</tr>
<tr>
<td>4</td>
<td>(S,S)-L2</td>
<td>-30</td>
<td>45</td>
<td>51</td>
<td>90</td>
<td>42</td>
<td>R</td>
</tr>
<tr>
<td>5</td>
<td>(S,R,R)-L3</td>
<td>-30</td>
<td>45</td>
<td>46</td>
<td>76</td>
<td>40</td>
<td>R</td>
</tr>
<tr>
<td>6</td>
<td>(S,S,S)-L3</td>
<td>-30</td>
<td>90</td>
<td>19</td>
<td>12</td>
<td>3</td>
<td>R</td>
</tr>
<tr>
<td>7</td>
<td>(S,R)-L4</td>
<td>-30</td>
<td>45</td>
<td>55</td>
<td>84</td>
<td>14</td>
<td>R</td>
</tr>
<tr>
<td>8</td>
<td>(S,S)-L4</td>
<td>-30</td>
<td>60</td>
<td>62</td>
<td>75</td>
<td>6</td>
<td>R</td>
</tr>
<tr>
<td>9</td>
<td>(S,R)-L5</td>
<td>-30</td>
<td>60</td>
<td>54</td>
<td>87</td>
<td>19</td>
<td>R</td>
</tr>
<tr>
<td>10</td>
<td>(S,S)-L5</td>
<td>-30</td>
<td>60</td>
<td>23</td>
<td>14</td>
<td>3</td>
<td>R</td>
</tr>
<tr>
<td>11</td>
<td>(S)-L6</td>
<td>-30</td>
<td>90</td>
<td>27</td>
<td>22</td>
<td>5</td>
<td>R</td>
</tr>
</tbody>
</table>

(a) Configuration of unreacted enone 7.5. (b) The values given in bold in the tables throughout this chapter are the first points at which an ee of 99% or higher was measured, which does not necessarily mean that this ee was not reached at lower conversion.
A first observation is that there is a good correlation between the performance of ligands in the asymmetric 1,4-addition and their performance in the kinetic resolution, i.e. the best ligands in the enantioselective 1,4-addition to 2-cyclohexenone, (S,R,R)-L1, (S,R)-L2, (S,S)-L2, and (S,R,R)-L33 are also the best ligands for the kinetic resolution of 7.5. Also noteworthy is that (S,R,R)-L1 gave a much faster reaction at −40 °C than all other ligands at −30 °C, reaching 48% conversion after only 15 min. Resolution experiments with (S,R,R)-L1 at −30 °C gave approximately the same selectivity, but were too fast to be accurately followed in time, giving over 50% conversion after just 5 min. Especially the large rate difference between the reactions in the presence the structurally very related (S,R,R)-L1 and (S,R)-L4, where only one methyl is replaced by a hydrogen, is remarkable (compare entries 1 and 7). In all cases a matched-mismatched effect was observed. In most cases the matched combination is the combination of (S)-BINOL and the R configuration in the amine part, e.g. (S,S,S)-L1 only gave s = 24 compared to the selectivity of 120 for (S,R,R)-L1. The ee’s obtained in the 1,4-addition of Et2Zn to 2-cyclohexenone with these ligands were 91% and >98%, respectively. (see Chapter 2). The most extreme case can be found in L3, were the S,R,R diastereomer gave 46% conversion after 45 minutes with s = 40 whereas the use of (S,S,S)-L3 gave an extremely sluggish reaction with s = 3 (see entries 5 and 6 and Figure 7.4).

![Figure 7.4](image-url) 

**Figure 7.4** Ee vs. conversion at t = 2, 5, 10, 15, 30, 45, 60, 75, and 90 min for the Et2Zn addition to 7.5 according to Scheme 7.11 in the presence of (S,R,R)-L3 (—) and (S,S,S)-L3 (—).

The difference between the matched and mismatched combinations in L2 is very small. The selectivities are comparable but in this case the reaction in the presence of (S,S)-L2 was faster than that in the presence of its diastereomer (entries 3 and 4). L4 and L5 also displayed significant differences in the selectivity between the diastereomers, although less extreme
than in the case of \( L_3 \). \( L_6 \), which has no chirality in the amine part, gave a relatively slow reaction with low selectivity.

In preliminary experiments, TADDOL based phosphoramidites \( L_7 \) and \( L_8 \) and \( C_2 \) symmetric BINOL phosphoramidite \( L_9 \) were also tested in the kinetic resolution of 7.5. (Figure 7.5). In these experiments, 7.5 was allowed to react with approximately 0.5 equivalents of Et\(_2\)Zn at \(-30\) °C after which the ee of 7.5 was determined. From the results it became clear that neither \( L_8 \) nor \( L_9 \) are suitable for this purpose, giving almost no conversion after 1 h and displaying low selectivities. Both ligands are probably too bulky around the phosphorus, making it difficult for 7.5 to coordinate to the copper in the catalytic complex. It is well known that for phosphoramidites based on TADDOL, a smaller amine unit gives a better result than a more bulky one in the 1,4-addition to cyclic enones.\(^{34}\) \((R,R)-L_7\) did give a reasonable selectivity (29% ee at \(-45\)% conversion) but these preliminary results did not justify further studies into these ligands.

![Figure 7.5 TADDOL phosphoramidites L7 and L8 and C2 symmetric BINOL phosphoramidite L9.](image)

### 7.3.3 Resolution of 7.5 on a multigram scale

The combination of high activity and selectivity makes \((S,R,R)-L_1\) the ligand of choice in the kinetic resolution of 7.5. This combination should make it possible to perform this kinetic resolution on a synthetically interesting scale. To demonstrate this, a resolution experiment was performed starting with 11.0 g (100 mmol) 7.5, using only 18.1 mg (0.05 mol%) Cu(OTf)\(_2\) and 54 mg (0.1 mol%) \((S,R,R)-L_1\) in toluene at \(-30\) °C. Addition of 0.55 equivalent of Et\(_2\)Zn gave 55% conversion after 20 h. Aqueous workup yielded a mixture of unreacted \((R)\)-7.5, 7.20, and \( n\)-dodecane (internal standard). By column chromatography 3.6 g (33%) of \((R)\)-7.5 was isolated with ee \(>99\)% (chiral GC). Product 7.20 was also isolated and comparison of the recorded \(^{13}\)C-NMR spectrum with literature data showed that this indeed consisted for \(>95\)% of the \textit{trans} isomer.\(^{35}\) The somewhat diminished isolated yield of \((R)\)-7.5 (33% out of a possible 45%) was caused by the volatility of 7.5, which resulted in loss of products during the evaporation of toluene, even if it was azeotropically removed in the presence of MeOH. A possible way to circumvent this problem would be to use more volatile solvents in this reaction. For this purpose a kinetic resolution experiment was performed under the standard conditions, using dichloromethane instead of toluene. Dichloromethane was chosen as a possible alternative because it gives results comparable to toluene in the “normal” asymmetric 1,4-addition.\(^{36}\) Indeed a good selectivity was observed, though lower
than with toluene (85% ee at 50% conversion, $s = 33$). Nevertheless, this could still be a viable alternative, if the loss of selectivity is outweighed by the easier isolation of unreacted $7.5$.

### 7.3.4 Kinetic resolution of 7.5 with different zinc reagents

We next turned our attention to the influence of the nature of the dialkylzinc reagent on the enantioselectivity in the kinetic resolution. In addition to Et$_2$Zn we therefore tested other commercially available zinc reagents like $i$-Pr$_2$Zn, $n$-Bu$_2$Zn, and Me$_2$Zn in the kinetic resolution of $7.5$ in the presence of ($S$,$R$,$R$)-L1 (Scheme 7.12).

![Scheme 7.12 Kinetic resolution of 7.5 with different zinc reagents.](image)

Initially, we anticipated that the use of the more bulky $i$-Pr$_2$Zn in the resolution of $7.5$, an even higher selectivity for the trans-product would be observed compared to Et$_2$Zn and consequently would give a higher $s$ value. However, when the reaction was performed under the standard conditions with the use of ($S$,$R$,$R$)-L1, just the opposite was observed: a dramatic decrease in selectivity to $s = 14$ (Table 7.2, entry 2). A parallel for this drop in selectivity can be found in the lower ee obtained in the 1,4-addition of $i$-Pr$_2$Zn to 2-cyclohexenone compared to the 1,4-addition of Et$_2$Zn (94% and >98% ee, respectively).$^{32}$

![Table 7.2 Kinetic resolution of 7.5 with different zinc reagents.](table)

<table>
<thead>
<tr>
<th>entry</th>
<th>$R$</th>
<th>equiv. of $R_2$Zn</th>
<th>$T$ (°C)</th>
<th>$t$ (min.)</th>
<th>convn. (%)</th>
<th>ee (%)</th>
<th>$s$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et</td>
<td>0.8</td>
<td>−40</td>
<td>15</td>
<td>48</td>
<td>88</td>
<td>120</td>
</tr>
<tr>
<td>2</td>
<td>$i$-Pr</td>
<td>0.8</td>
<td>−30</td>
<td>60</td>
<td>55</td>
<td>84</td>
<td>14</td>
</tr>
<tr>
<td>3</td>
<td>$n$-Bu</td>
<td>0.8</td>
<td>−35</td>
<td>15</td>
<td>49</td>
<td>93</td>
<td>&gt;200</td>
</tr>
<tr>
<td>4</td>
<td>Me</td>
<td>1.0</td>
<td>−35</td>
<td>20</td>
<td>50</td>
<td>93</td>
<td>94</td>
</tr>
</tbody>
</table>

On the other hand the use of 0.8 equivalents of $n$-Bu$_2$Zn led to a significant increase in selectivity to give $s > 200$ (entry 3). This means that an ee of of 99% can be reached at only 51% conversion.$^{37}$ It is not easy to explain this increase in selectivity, since the $n$-Bu$_2$Zn also gave a lower ee in the 1,4-addition to 2-cyclohexenone compared to Et$_2$Zn. Maybe the increase in selectivity can be explained by an increase in the $trans$-selectivity in the 1,4-addition, since Sato et al. reported an extremely high $trans:cis$ selectivity of $>99:1$ for the addition of $n$-BuCu(CN)Li to $7.5$.$^{8c}$ The results for the kinetic resolution of $7.5$ with different
zinc reagents are graphically summarized in Figure 7.6. A peculiar observation was made in the case of Me₂Zn. Figure 7.6 shows that at the beginning of the reaction the selectivity in the resolution of 7.5 is somewhat lower than observed for Et₂Zn and n-Bu₂Zn, but an increase is observed just before 50% conversion. This rise in selectivity could be due to a change in the kinetics of this reaction with increasing conversion. Further kinetic studies are required to prove that this is the proper explanation for this observation.

![Figure 7.6](image)

**Figure 7.6** Ee vs. conversion for the resolution of 7.5 with Et₂Zn (- ■ -), i-Pr₂Zn (- ▼ -), n-Bu₂Zn (- ● -) or Me₂Zn (- ▲ -) (Scheme 7.12 and Table 7.2).

From Figure 7.7, a plot of conversion against time, it becomes clear that the selectivity is indeed much higher than is indicated by the calculated value of \( s = 94 \), since the reaction virtually stops at just over 50% conversion in the presence of 1 equivalent of Me₂Zn. Also striking is the fact that the reaction is relatively fast for \((R)-7.5\), since the reaction of Me₂Zn with 2-cyclohexenone under identical conditions is notoriously slow. Experiments performed in our group by undergraduate student Richard Jagt showed that the 1,4-addition of Me₂Zn to enantiomerically pure \((R)-7.5\) in the presence of \((S,R,R)-L1\), i.e. the mismatched combination between substrate and ligand, was extremely sluggish with a reaction time of approximately 4 days and a \(cis:trans\) ratio of 30:70. In contrast, reaction in the presence of the opposite enantiomer, \((R,S,S)-L1\), proceeded rapidly with complete selectivity for the \(trans\) compound.
7.4 Kinetic resolution of 5-isopropyl- and 5-phenyl-2-cyclohexenone

To investigate whether the copper-phosphoramidite catalyzed kinetic resolution of 5-substituted 2-cyclohexenones can be seen as a general method to obtain these compounds enantiomerically pure, more substrates needed to be tested. Therefore racemic 5-isopropyl-2-cyclohexenone (7.21) and 5-phenyl-2-cyclohexenone (7.22) were synthesized in two steps with good yields from 5-isopropyl-1,3-cyclohexanedione and 5-phenyl-1,3-cyclohexanedione, respectively.40

\[ R = \text{i-Pr} \]
\[ R = \text{Ph} \]

**Scheme 7.13** Synthesis of 5-isopropyl- and 5-phenyl-2-cyclohexenone.

7.4.1 Kinetic resolution of 5-isopropyl-2-cyclohexenone (7.21)

The resolution experiments for 7.21 were performed under the standard conditions used for the kinetic resolution of 7.5 and the ee and conversion could again be determined in one run.
using chiral GC (Scheme 7.14). The results for these resolution experiments are summarized in Table 7.3. Again, the best result for the kinetic resolution of 7.21 with Et₂Zn was found using 2 mol% of (S,R,R)-L1 and 1 mol% of Cu(OTf)₂ at −40 °C in toluene. Under these conditions a good selectivity ($s = 39$) was found, reaching 96% ee at 54% conversion. The lower selectivity as compared to 7.5 under the same conditions indicates that increase of steric bulk in the substrate does not necessarily lead to higher selectivity.

When comparing the other results obtained with ligand L1-L4 (entries 1-8 in Table 7.3) with the results obtained for 7.5 (Table 7.1), the same general trend can be observed. The only significant difference is that there is a more pronounced matched-mismatched effect between (S,R)-L2 and (S,S)-L2 with this substrate than with 7.5. Also noteworthy is that (S,R,R)-L3 gave a selectivity in the same order of magnitude as (S,R,R)-L1, although the reaction was again much slower with this ligand.

**Scheme 7.14 Kinetic resolution of 5-isopropyl-2-cyclohexenone (7.21).**

<table>
<thead>
<tr>
<th>entry</th>
<th>ligand</th>
<th>R</th>
<th>T (°C)</th>
<th>t (min.)</th>
<th>convn. (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(S,R,R)-L1</td>
<td>Et</td>
<td>−40</td>
<td>10</td>
<td>54</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>(S,S,S)-L1</td>
<td>Et</td>
<td>−30</td>
<td>75</td>
<td>58</td>
<td>78</td>
</tr>
<tr>
<td>3</td>
<td>(S,R)-L2</td>
<td>Et</td>
<td>−30</td>
<td>15</td>
<td>45</td>
<td>67</td>
</tr>
<tr>
<td>4</td>
<td>(S,S)-L2</td>
<td>Et</td>
<td>−30</td>
<td>45</td>
<td>52</td>
<td>63</td>
</tr>
<tr>
<td>5</td>
<td>(S,R,R)-L3</td>
<td>Et</td>
<td>−30</td>
<td>30</td>
<td>46</td>
<td>74</td>
</tr>
<tr>
<td>6</td>
<td>(S,S,S)-L3</td>
<td>Et</td>
<td>−30</td>
<td>90</td>
<td>46</td>
<td>36</td>
</tr>
<tr>
<td>7</td>
<td>(S,R)-L4</td>
<td>Et</td>
<td>−30</td>
<td>60</td>
<td>61</td>
<td>86</td>
</tr>
<tr>
<td>8</td>
<td>(S,S)-L4</td>
<td>Et</td>
<td>−30</td>
<td>90</td>
<td>57</td>
<td>59</td>
</tr>
<tr>
<td>9</td>
<td>(S,R,R)-L1</td>
<td>Me</td>
<td>−35</td>
<td>25</td>
<td>48</td>
<td>85</td>
</tr>
<tr>
<td>10</td>
<td>(S,R,R)-L1</td>
<td>n-Bu</td>
<td>−35</td>
<td>60</td>
<td>50</td>
<td>93</td>
</tr>
</tbody>
</table>

Resolution of racemic 7.21 on a 1 g scale using Et₂Zn, Cu(OTf)₂ and (S,R,R)-L1 yielded enantiomerically pure starting material in 32% yield. Since the specific optical rotation of neither of the enantiomers of 7.21 has been reported, the absolute configuration of the remaining starting material was tentatively assigned based on analogy with the results
reported in this chapter. Both the use of Me₂Zn and n-Bu₂Zn led to a significant increase in selectivity, the highest (calculated) selectivity ($s = 94$) being obtained with n-Bu₂Zn. A plot of the conversion against time for the resolutions with these three zinc reagents shows that the reaction performed with 0.8 equivalents of Me₂Zn virtually stops at just over 50% conversion, indicating a higher selectivity than the calculated $s = 66$ (see also Section 7.3.3).

![Figure 7.8](image.png)

**Figure 7.8** Conversion vs. time for the resolution of 7.21 with Et₂Zn (-●-), n-Bu₂Zn (-○-) or Me₂Zn (-▲-) (Scheme 7.14 and Table 7.3).

### 7.4.2 Kinetic resolution of 5-phenyl-2-cyclohexenone (7.22)

Because the ee of 5-phenyl-2-cyclohexenone (7.22) could not be determined by GC, a different method was used to perform the copper-phosphoramidite catalyzed kinetic resolution of this substrate. Racemic 7.22 was allowed to react with 0.55 equivalent of Et₂Zn to give 55% conversion (checked by GC) after which the reaction was quenched.

![Scheme 7.15](image.png)

**Scheme 7.15** Kinetic resolution of 7.22.
Enantiomerically enriched 7.22 was isolated by column chromatography in 38% yield and the ee determined by chiral HPLC (Scheme 7.15). Comparison of the optical rotation with the literature value showed that the unreacted 7.22 had the expected R configuration. With $s = 19$ this resolution is considerably less efficient than the resolution of alkyl substituted 2-cyclohexenones 7.5 and 7.21, but it is still high enough to be useful. It is possible, or even likely, that the selectivity can be improved by using $n$-Bu$_2$Zn or Me$_2$Zn, but these experiments were not performed.

### 7.5 Kinetic resolution of 5-trimethylsilyl-2-cyclohexenone

As was mentioned in Section 7.1, 5-trimethylsilyl-2-cyclohexenone (7.6) is an important and versatile building block from which a variety of other enantiomerically pure 5-substituted 2-cyclohexenones can readily be synthesized. Racemic 7.6 can be synthesized in 3 steps from anisole according to a literature procedure as is shown in Scheme 7.16.

**Scheme 7.16 Synthesis of racemic 5-trimethylsilyl-2-cyclohexenone.**

An alternative to the Corey approach to obtain building block 7.6 in enantioenriched form was already published in 1987 by Asaoka et al. (Scheme 7.17).

**Scheme 7.17 Kinetic resolution of 7.6 through the asymmetric 1,4-addition of thiols as reported by Asaoka et al.**

Their method is related to the method developed by us in that it uses the well known catalytic asymmetric 1,4-addition of thiols to carry out a kinetic resolution on racemic 7.6. When racemic 7.6 is treated with 0.55 equivalents of $p$-toluenethiol in the presence of a catalytic amount of the alkaloid (−)-cinchonidine, (S)-7.6 can be obtained in 41% yield with
59% ee, which indicates that the selectivity is only moderate. More importantly, \((R,R)-7.24\) can be isolated in 50% with 57% ee and can be recrystallized to enantiomeric purity. Elimination of the thiol under basic conditions will yield enantiomerically pure \((R)-7.6\). As usual, a major drawback of this method is that it is rather tedious, consisting of a modestly selective kinetic resolution step followed by recrystallization and elimination of the thiol.

The results of the first kinetic resolution experiments carried out with racemic \(7.6\) and \(Et_2Zn\) were somewhat disappointing (Scheme 7.18). Using the standard conditions, \(i.e.\) 2 mol\% \((S,R,R)-L1\), 1 mol\% Cu(OTf)_2, 0.8 equivalents of \(Et_2Zn\) in toluene at \(-30\) °C, 86% ee was reached at 56% conversion (entry 1, Table 7.4). The use of both diastereomers of \(L2\) revealed that \((S,R)-L2\) displayed a similar selectivity whereas \((S,S)-L2\) gave a considerably slower reaction with low selectivity.

\[
\begin{align*}
\text{Scheme 7.18 Kinetic resolution of 5-trimethylsilyl-2-cyclohexenone (7.6).}
\end{align*}
\]

This makes the resolution shown in Scheme 7.18 considerably less selective than the resolutions carried out under the same conditions on both \(7.5\) and \(7.21\). Change of the organozinc reagent to \(Me_2Zn\) or \(n-Bu_2Zn\), however, proved to be highly beneficial. With the use of \(n-Bu_2Zn\) the selectivity increased and gave a nearly perfect resolution \((s > 200, entry 5)\). This is the largest increase in selectivity observed by just changing the zinc reagent. Note that with such a high selectivity the product \(7.25\) \((R = n-Bu)\) can be obtained with a high ee. This allows for isolation of 5-\(n\)-butyl-2-cyclohexenone \((7.12)\) with high ee after elimination of the trimethylsilyl group,\(^{41}\) thus making both product and unreacted starting material synthetically interesting.

<table>
<thead>
<tr>
<th>entry</th>
<th>R</th>
<th>equiv. of (R_2Zn)</th>
<th>ligand</th>
<th>T</th>
<th>t</th>
<th>convn. (%)</th>
<th>ee</th>
<th>s</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et</td>
<td>0.8</td>
<td>((S,R,R)-L1)</td>
<td>-30</td>
<td>5</td>
<td>56</td>
<td>86</td>
<td>14</td>
</tr>
<tr>
<td>2</td>
<td>Et</td>
<td>0.8</td>
<td>((S,R)-L2)</td>
<td>-30</td>
<td>30</td>
<td>57</td>
<td>86</td>
<td>13</td>
</tr>
<tr>
<td>3</td>
<td>Et</td>
<td>0.8</td>
<td>((S,S)-L2)</td>
<td>-30</td>
<td>60</td>
<td>57</td>
<td>31</td>
<td>2</td>
</tr>
<tr>
<td>4</td>
<td>Me</td>
<td>1.0</td>
<td>((S,S,R)-L1)</td>
<td>-35</td>
<td>15</td>
<td>50</td>
<td>90</td>
<td>58</td>
</tr>
<tr>
<td></td>
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<td></td>
<td></td>
<td>25</td>
</tr>
<tr>
<td>5</td>
<td>(n-Bu)</td>
<td>0.8</td>
<td>((S,R,R)-L1)</td>
<td>-35</td>
<td>25</td>
<td>48</td>
<td>94</td>
<td>&gt;200</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>&gt;99</td>
</tr>
</tbody>
</table>
The results of the kinetic resolution of 7.6 with different zinc reagents are graphically summarized in Figure 7.4. Resolution on a 5 mmol scale using $n$-Bu$_2$Zn allowed the isolation of 2.2 mmol of enantiomerically pure 7.6. The absolute configuration of the unreacted starting material ($R$) was determined by comparing the measured optical rotation with the literature values.\(^7\)

![Figure 7.9 Conversion vs. time for the resolution of 7.6 with Et$_2$Zn (-■-), $n$-Bu$_2$Zn (-○-) or Me$_2$Zn (-▼-) (Scheme 7.16 and Table 7.4).](image)

### 7.6 Kinetic resolution of various other substrates

#### 7.6.1 Kinetic resolution of 4-methyl-2-cyclohexenone (7.4)

Racemic 4-methyl-2-cyclohexenone (7.4) can also be synthesized from cheap starting materials in a one step procedure\(^29\) and was therefore also tested in the phosphoramidite catalyzed kinetic resolution. As mentioned in Section 7.1, enantiomerically pure 7.4 is a building block used in the synthesis of various natural compounds.\(^44\)

![Scheme 7.19 Kinetic resolution of 4-methyl-2-cyclohexenone (7.4).](image)
All resolution experiments were carried out under standard conditions (Scheme 7.19) and the results are summarized in Table 7.5. The results demonstrate that the resolution of 7.4 is much less selective than the resolution of 7.5. With the use of 0.8 equivalents of Et₂Zn, 1 mol% Cu(OTf)₂, 2 mol% (S,R,R)-L₁ at −40 °C a selectivity of 16 is reached compared to $s = 120$ with 7.5 under identical conditions. The lower selectivity is not unexpected since it is generally known that additions to 4-substituted-2-cyclohexenones proceed with a lower trans/cis ratio than conjugate additions to 5-substituted-2-cyclohexenones.³⁵,⁴⁵ Another reason may be that the use of (S,R,R)-L₁ gives a lower ee in the 1,4-addition of Et₂Zn to 5,5-dimethyl-2-cyclohexenone compared to 4,4-dimethyl-2-cyclohexenone (88% and >98%, respectively, see Chapter 3).⁴⁶ These results indicate that the catalyst experiences more hindrance from the two methyl groups at the 5 position (1,3-diaxial interactions in the transition state) than from those at the 4 position. Although the 1,3-diaxial effect has a negative influence on the enantioselectivity in the 1,4-addition, a positive effect may occur in the kinetic resolution, where only one methyl is present in the substrate. With one methyl group attack is possible trans to the methyl group. Thus the combination of the intrinsic trans selectivity in the 1,4-addition to substituted 2-cyclohexenones (see paragraph 7.3) are increased by the stereospecific steric interactions between substrate and catalyst. Since these interactions are stronger in the case of 7.5 compared to 7.4, a lower selectivity can be expected for 7.4.

Table 7.5 Kinetic resolution of 7.4 under standard conditions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>ligand</th>
<th>T (°C)</th>
<th>t (min.)</th>
<th>convn. (%)</th>
<th>ee (%)</th>
<th>$s$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Et</td>
<td>(S,R,R)-L₁</td>
<td>−40</td>
<td>15</td>
<td>48</td>
<td>71</td>
<td>16</td>
</tr>
<tr>
<td>2</td>
<td>Et</td>
<td>(S,S,S)-L₁</td>
<td>−30</td>
<td>60</td>
<td>55</td>
<td>83</td>
<td>13</td>
</tr>
<tr>
<td>3</td>
<td>Et</td>
<td>(S,R,R)- + (S,S,S)-L₁</td>
<td>−30</td>
<td>30</td>
<td>52</td>
<td>78</td>
<td>17</td>
</tr>
<tr>
<td>4</td>
<td>Et</td>
<td>(S,R)-L₂</td>
<td>−30</td>
<td>105</td>
<td>57</td>
<td>81</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>Et</td>
<td>(S,S)-L₂</td>
<td>−30</td>
<td>75</td>
<td>56</td>
<td>85</td>
<td>13</td>
</tr>
<tr>
<td>6</td>
<td>Et</td>
<td>(S,R,R)-L₃</td>
<td>−30</td>
<td>105</td>
<td>54</td>
<td>83</td>
<td>15</td>
</tr>
<tr>
<td>7</td>
<td>Et</td>
<td>(S,S,S)-L₃</td>
<td>−30</td>
<td>120</td>
<td>19</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>8</td>
<td>Me</td>
<td>(S,R,R)-L₁</td>
<td>−35</td>
<td>75</td>
<td>58</td>
<td>82</td>
<td>10</td>
</tr>
<tr>
<td>9</td>
<td>n-Bu</td>
<td>(S,R,R)-L₁</td>
<td>−35</td>
<td>25</td>
<td>45</td>
<td>70</td>
<td>27</td>
</tr>
</tbody>
</table>

The results obtained with other ligands again show that (S,R,R)-L₁ is the best ligand for the resolution of 7.4. However, the peculiar observation was made that (S,S,S)-L₁ performed nearly as well ($s = 13$), whereas the resolution with a 1:1 mixture of the two diastereomers of L₁ gave a selectivity of 17 (entry 3). The use of Me₂Zn did not have a beneficial effect in this case, decreasing the selectivity to $s = 10$. The use of n-Bu₂Zn did increase the selectivity to $s = 27$, which makes the copper-phosphoramidite catalyzed resolution of this substrate also synthetically useful. In all cases the remaining substrate had the S configuration as was
determined by comparing the measured optical rotation of an isolated sample with the literature value.\textsuperscript{5a}

A very nice alternative to obtain enantiomerically enriched 7.4 by kinetic resolution was developed by Bertozzi \textit{et al.} in cooperation with our group.\textsuperscript{47} The key step of this procedure is the copper-phosphoramidite catalyzed enantioselective addition of Me\textsubscript{2}Zn to racemic vinyl epoxide 7.26 using (R,R,R)-L\textsubscript{1} (Scheme 7.20).

![Scheme 7.20](image)

**Scheme 7.20** Kinetic resolution of 7.26 to give both (R)- and (S)-7.4 as reported by Bertozzi \textit{et al.}^47

By using 0.5 equivalent of Me\textsubscript{2}Zn, (1R,4R)-7.27 was isolated in 41\% yield and oxidation of the alcohol with PDC gave (R)-7.4 with 93\% ee. A nice feature is that the unreacted starting material (1S,2R)-7.26 can be used in a second Me\textsubscript{2}Zn addition in the presence (S,S,S)-L\textsubscript{1} to give (S)-7.4 with 94\% ee after PDC oxidation, making very efficient use of the starting material. The authors also indicate that the use of other zinc reagents could make the synthesis of a whole range of enantiomerically enriched 4-substituted 2-cyclohexenones possible.

### 7.6.2 Kinetic resolution of 6-methyl-2-cyclohexenone (7.28)

6-Methylcyclohexenone (7.28, see Figure 7.10)\textsuperscript{29} was also tested in the copper-phosphoramidite catalyzed kinetic resolution.

![Figure 7.10](image)

**Figure 7.10** Chiral 2-cyclohexenones 7.28 and 7.29.
As expected, hardly any selectivity was observed. We found only 6% ee at 65% conversion ($s = 1.1$) using 0.8 equivalents of Et$_2$Zn, 1 mol% Cu(OTf)$_2$ and 2 mol % ($S,R,R$)-L1 in toluene at $-40 \, ^\circ\text{C}$. In this case the stereogenic centre is probably just too far away from the reaction site to effect stereodifferentiation.$^{48}$ Therefore, no further experiments were performed with this substrate.

### 7.6.3 Kinetic resolution of 4-acetoxy-2-cyclohexenone (7.29)

Initial kinetic resolution experiments were performed on the readily available and synthetically interesting 4-acetoxy-2-cyclohexenone (7.29)$^{49,50}$ A rapid reaction took place with almost all of the Et$_2$Zn being consumed after 15 min, when racemic 7.29 was allowed to react with approximately 0.6 equivalents of Et$_2$Zn in the presence of 1 mol% Cu(OTf)$_2$ and 2 mol% ($S,R,R$)-L1 in toluene at $-30 \, ^\circ\text{C}$. At this point the ee was only 43%, showing that the selectivity for this substrate was moderate. A possible explanation for this low selectivity is that a fast blank reaction between 7.29 and Et$_2$Zn in the absence of a copper catalyst. An oxygen catalyzed 1,4-addition of Et$_2$Zn to the structurally related substrate 7.30 has been reported by Hanneke van der Deen in our group (Scheme 7.21)$^{51}$

![Scheme 7.21 Air induced 1,4-addition of Et$_2$Zn as reported by van der Deen.](image)

Control experiments, in which 7.29 was allowed to react with Et$_2$Zn in toluene at $-30 \, ^\circ\text{C}$, without the exclusion of air, did not give any reaction according to GC. Even at room temperature no blank reaction was observed, demonstrating that an air induced blank reaction is not the explanation for the low selectivity. These preliminary results indicate that 7.29 is not a very good substrate, possibly because of coordination of the oxygen subsituent(s) to the copper, which could lower the selectivity. Such an oxygen directing effect has been observed in the 1,4-addition to 4-alkoxy-4-alkyl-2-cyclohexadienones.$^{52}$ No convenient routes to racemic 2-cyclohexenones with an oxygen substituent on the 5-position are known and therefore such substrates were not tested (see Section 7.2).

### 7.7 Conclusions and discussion

The work described in this chapter demonstrates that the copper-phosphoramidite catalyzed kinetic resolution using ($S,R,R$)-L1 is highly selective for several chiral racemic 2-
cyclohexenones. Selectivities up to and over 200 have been reached for the important building blocks 7.5 and 7.6. Other 5-substituted-2-cyclohexenones, such as 7.21 and 7.22 also gave reasonable to good selectivities ranging from 19 to 94. Since both enantiomers of the phosphoramidite catalysts are readily available, both enantiomers of the desired chiral 2-cyclohexenone building blocks are accessible. Kinetic resolution of 4-methyl-2-cyclohexenone (7.4) gave a lower selectivity, but can still be useful.

Since in most cases the racemates of the chiral 2-cyclohexenones described in this chapter are readily prepared from cheap starting materials and alternative routes to obtain these chiral 2-cyclohexenones enantiomerically pure are not (always) very practical, the highly selective kinetic resolution procedure described in this chapter provides a valuable alternative. The resolution of 100 mmol of racemic 7.5 with 0.05 mol% of Cu(OTf)2 and 0.1 mol% (S,R,R)-L1 demonstrates the synthetic applicability of the procedure.

For large scale resolutions, isolation of the starting material by column chromatography is not the ideal method. A possible alternative is separation by distillation but this could be complicated by the small difference in boiling point of starting material and product. To improve this, it might be interesting to perform the kinetic resolution in the presence of e.g. benzaldehyde, trapping the formed zinc enolate in an aldol reaction (see Chapter 1). The boiling point of the aldol products is sufficiently high to allow easy separation by distillation.

A further improvement of the methodology presented in this chapter would be the development of a catalytic system that introduces a nucleophile to the 2-cyclohexenone that can be eliminated afterwards (e.g. thiols, see Scheme 7.17), with the same selectivity as the copper-phosphoramidite systems. One option would be the introduction of a silyl group via a 1,4-addition.53 This would enable the isolation of both enantiomers of the chiral cyclohexenone with high ee after elimination of the silyl group from the product (Scheme 7.22).

![Scheme 7.22 Proposed kinetic resolution through the 1,4-addition of silyl zinc reagents.](image-url)
Additionally, copper-phosphoramidite catalysts might also be applied in the resolution of chiral cycloalkenones with different ring sizes, chiral α,β-unsaturated lactones, and chiral linear enones.

7.8 Experimental section

For general remarks see previous chapters. All resolution experiments were performed in flame dried glassware under an argon atmosphere. Racemic substrates 7.4, 7.5, and 7.28, 7.21 and 7.22, 7.6, and 7.29 were prepared according to literature procedures. i-Pr2Zn and n-Bu2Zn solutions in toluene and L2-L6 were kindly provided by Leggy Arnold. Ligands L7, L8 and L9 were synthesized by A. Mandoli. Both of them are gratefully acknowledged.

**General procedure for the kinetic resolution of 7.4, 7.5, 7.6, 7.21, 7.28 on an analytical scale**

All resolution were performed on a 1 mmol scale with 1 mol% Cu(OTf)2 and 2 mol% of the phosphoramidite ligand with n-dodecane as internal standard.

Typical experimental procedure for the resolution of racemic 7.5; Cu(OTf)2 (3.6 mg, 0.01 mmol) and (S,R,R)-L1 (10.8 mg, 0.02 mmol) were dissolved in dry toluene (10 ml). After stirring at RT for 1 h the colorless solution was cooled to −40°C and racemic 7.5 (110 mg, 1.0 mmol) and n-dodecane (40 µL, internal standard) were added. After stirring for about 1 min a sample of 0.2 ml was taken (t=0) and treated as usual (*vide infra*). After stirring for an additional 10 min, Et2Zn (0.73 ml, 1.1 M in toluene, 0.8 mmol) was added. Samples of 0.2 ml were taken after 2, 5, 10, 15, 20, 25, 30, 45, and 60 minutes. The samples were quenched with 1 ml Et2O saturated with water and filtered over a small plug of silica. The silica plugs were rinsed with 4 × 1 ml of the wet ether. Both conversion, relative to the internal standard, and ee were determined by chiral GC. Chiraldex G-TA, 50 m × 0.25 mm, He-flow: 1.0 ml/min, 100°C isotherm. \( t_{ret} \) 13.4 min (n-dodecane), \( t_{ret} \) 21.6 min (S-7.5), \( t_{ret} \) 22.7 min (R-7.5).

**Determination of conversion and ee for 7.5**

In all cases ee and conversion were determined by GC on a Chiraldex G-TA column (*vide supra*) except for the resolution performed with Me2Zn. In this case the peaks of (S)-7.5 and the addition product overlapped. Ee and conversion were therefore measured on a Chiraldex A-TA column.

**Determination of conversion and ee for 7.21**

Ee and conversion were determined by GC on a Hydrodex-B-3P column, 25 m × 0.25 mm, He-flow: 0.9 ml/min. Initial temp: 90°C, initial time: 10 min, rate: 5°C/min, final temp: 150°C. \( t_{ret} \) 17.5 min (n-dodecane), \( t_{ret} \) 21.9 min (S-7.21), \( t_{ret} \) 22.1 min (R-7.21).
Determination of conversion and ee for 7.6
Ee and conversion were determined by GC on a CP-Chirasil-Dex CB column, 25 m × 0.25 mm, He-flow: 1.0 ml/min. Initial temp: 125°C, initial time: 20 min, rate: 10°C/min, final temp: 175°C. tret 6.0 min (n-dodecane), tret 10.9 min ((S)-7.6), tret 11.4 min ((R)-7.6).

Determination of conversion and ee for 7.4
Ee and conversion were determined by GC on a Chiraldex G-TA column, 50 m × 0.25 mm, He-flow: 1.0 ml/min, 100°C isothermic. tret 13.4 min (n-dodecane), tret 20.1 min ((R)-7.4), tret 20.8 min ((S)-7.4). Resolution on a 1.0 g scale under standard conditions (vide infra) allowed the isolation of 120 mg (1.09 mmol, 12%, procedure not optimized) of (S)-7.4 by column chromatography (SiO₂, hexanes-ether: 4-1): \[ \alpha \] = −110.8° (c = 1.11, CHCl₃), lit.: \[ \alpha \] = −113.0° (c = 1.14, CHCl₃).

Determination of conversion and ee for 7.28
Ee and conversion were determined by GC on a Chiraldex G-TA column, 50 m × 0.25 mm, He-flow: 1.0 ml/min, 100°C isothermic. tret 13.4 min (n-dodecane), tret 19.3 min (7.28), tret 21.0 min (7.28).

Determination of conversion and ee for 7.29
Ee was determined by GC on a Chiraldex G-TA column, 50 m × 0.25 mm, He-flow: 1.0 ml/min, 120°C isothermic. tret 27.0 min (7.29), tret 28.0 min (7.29).

Resolution of racemic 7.5 on 100 mmol scale
Cu(OTf)₂ (18 mg, 0.05 mmol) and (S,R,R)-L1 (54 mg, 0.10 mmol) were dissolved in 100 ml of dry toluene. After stirring at RT for 1 h the colorless solution was cooled to −30°C and racemic 7.5 (11.0 g, 100 mmol) and n-dodecane (4.0 ml) were added. After stirring for 10 min a sample was taken (t=0) after which Et₂Zn (50 ml, 1.1 M in toluene, 55 mmol) was added dropwise via a syringe over 5 min. A sample (0.1 ml) was taken after reaction overnight and analyzed by chiral GC (vide supra) showing 7.5 with 93% ee at 51% conversion. Additional Et₂Zn (3.6 ml, 1.1 M in toluene) was added and after 3 h another sample was taken. GC analysis showed >99% ee and 55% conversion. The reaction mixture was quenched with 150 ml of 1 M HCl (aq) and the aqueous layer was extracted with Et₂O (3 × 100 ml) and the combined organic layers were washed with brine and dried over Na₂SO₄. The drying agent was removed by filtration and the ether removed after which 150 ml MeOH was added. Further concentration yielded a mixture of 7.5, addition product and n-dodecane which were separated by column chromatography (SiO₂, hexanes:ether 4:1) giving 3.6 g (33 mmol, 33%) of (R)-(−)-7.5 as a colorless oil. \[ \alpha \] = −87.3° (c = 0.81, CHCl₃), lit.: \[ \alpha \] = −90.2° (c = 0.8, CHCl₃). ¹H-NMR (200 MHz, CDCl₃): δ 1.06 (d, J = 6.1 Hz, 3H), 1.9-2.5 (m, 5H), 6.0 (m, 1H), 6.9 (m, 1H). ¹³C-NMR (300MHz, CDCl₃): δ 21.06 (q), 30.20 (d), 33.87 (t), 46.12 (t), 129.44 (d), 149.80 (d), 199.93 (s). GC analysis (vide supra) showed ee >99% (no (S)-7.5 was detected).
Kinetic resolution of 7.21 on a 1.0 g scale

The resolution on 1.0 g (7.2 mmol) of 7.21 was performed using standard conditions using Cu(OTf)2 (5.2 mg, 0.014 mmol), (S,R,R)-L1 (15.1 mg, 0.028 mmol), n-dodecane (0.40 ml), and Et2Zn (4.0 ml, 1.1 M in toluene, 4.4 mmol) in toluene (20 ml) at −30 °C. After 60% conversion was reached, as checked by GC analysis, the reaction mixture was quenched with 20 ml saturated NH4Cl (aq) and the aqueous layer was extracted with Et2O (3 × 30 ml). The combined organic layers were washed with brine and dried over Na2SO4. Filtration and removal of the solvents yielded a mixture of 7.21, addition product and internal standard which were separated by column chromatography (SiO2, hexanes:ether 5:1) giving 321 mg (2.33 mmol, 32%) enantiomerically pure 7.21 as a colorless oil. [α]D = −39.2° (c = 1.60, CHCl3). 1H-NMR (300 MHz, CDCl3): δ 0.85 (d, J = 7.0 Hz, 6H), 1.5 (m, 1H), 1.8 (m, 1H), 2.1 (m, 2H), 2.4 (m, 2H), 5.93 (d, J = 9.9 Hz, 1H), 6.9 (m, 1H). 13C-NMR (300MHz, CDCl3): δ 19.35 (q), 19.43 (q), 29.48 (t), 31.91 (d), 41.41 (d), 41.80 (t), 129.45 (d), 150.36 (d), 200.53 (s). GC analysis (vide supra) showed ee >99%.

Kinetic resolution of 7.6 on a preparative scale

The resolution on 880 mg (5.2 mmol) of 7.6 was performed under standard conditions using Cu(OTf)2 (4.3 mg, 0.012 mmol), (S,R,R)-L1 (15.1 mg, 0.024 mmol), n-dodecane (0.40 ml, internal standard), and n-Bu2Zn (3.0 ml, ~1.0 M in toluene, 3.0 mmol) in toluene (20 ml) at −30 °C. After 54% conversion was reached, as checked by GC analysis, the reaction mixture was quenched with saturated NH4Cl (20 ml) and the aqueous layer was extracted with Et2O (3 × 30 ml). The combined organic layers were washed with brine and dried over Na2SO4. Filtration and removal of the solvents yielded a mixture of 7.6, addition product and internal standard which were separated by column chromatography (SiO2, hexanes:ether 5:1) giving 350 mg (2.08 mmol, 40%) of (R)-7.6 as a colorless oil. [α]D = −5.0° (c = 1.40, CHCl3), lit. for (S)-7.6: [α]D = −5.6° (c = 0.61, CHCl3). 1H-NMR (300 MHz, CDCl3): δ −0.03 (s, 9H), 1.3 (m, 1H), 2.1-2.4 (m, 4H), 5.9 (m, 1H), 7.0 (m, 1H). 13C-NMR (300MHz, CDCl3): δ −3.80 (q), 23.11 (d), 26.74 (t), 38.58 (t), 129.39 (d), 151.47 (d), 200.37 (s). GC analysis (vide supra) showed ee >99%.

Procedure for the kinetic resolution of 7.22

Cu(OTf)2 (10.5 mg, 0.03 mmol) and (S,R,R)-L1 (31.3 mg, 0.06 mmol) were dissolved in dry toluene (20 ml). After stirring at RT for 1 h the colorless solution was cooled to −35°C and racemic 7.22 (1.0 g, 5.8 mmol) and n-hexadecane (0.40 ml, internal standard) were added. After stirring for 10 min Et2Zn (2.85 ml, 1.1 M in toluene, 3.1 mmol) was added. After stirring overnight at −35°C a sample (0.2 ml) was taken. The sample was quenched in 1 ml of Et2O saturated with water and filtered over a small plug of silica. The silica plug was thoroughly rinsed with the wet Et2O. Analyses on a DB-1 (J&W) GC column showed that the conversion was 55%. The reaction mixture was quenched with 20 ml of 1N HCl (aq) and the aqueous layer was extracted with Et2O (3 × 25 ml) and the combined organic layers were washed with brine and dried over Na2SO4. Filtration and removal of the solvents yielded a
mixture of 7.22, addition product and n-hexadecane which were separated by column chromatography (SiO₂, hexanes-ether: 5-1) giving 378 mg (2.2 mmol, 38%) of (R)-(−)-7.22 as a colorless oil which solidified upon standing. \([\alpha]_D^0 = −37.9^\circ\) (c = 1.97, CHCl₃), lit.: \([\alpha]_D^0 = −46.4^\circ\) (c = 5.0, CHCl₃).\(^{\text{a}}\) \(^1\)H-NMR (200 MHz, CDCl₃): δ 2.5-2.8 (m, 4H), 3.4, (m, 1H), 6.1-6.2 (m, 1H), 7.0-7.1 (m, 1H), 7.2-7.4 (m, 5H). \(^{13}\)C-NMR (300MHz, CDCl₃): δ 33.64 (t), 40.91 (d), 44.81 (t), 126.64 (d), 126.94 (d), 128.72 (d), 129.73 (d), 143.13 (s), 149.47 (d), 199.15 (s). HPLC analysis (Chiralcel OJ, heptane-isopropanol: 95-5, flowrate 1.0 ml/min, \(\lambda_{\text{det}} = 220\text{ nm, } t_{\text{ret}} 11.7\) min ((R)-7.22), \(t_{\text{ret}} 14.3\) min ((S)-(7.22)) showed ee = 89%.

### 7.9 References and notes


3. For instance (R)-pulegone (85%) costs f 73,80/100 ml and (R)-pulegone (98%) f 94,30/5 g but (S)-pulegone (98%) costs f 274,-/1g. Prices are taken from the Aldrich catalogue 2000-2001.


Copper-phosphoramidite catalyzed kinetic resolution of chiral 2-cyclohexenones

19 Practice shows that rate laws for synthetically useful kinetic resolutions are almost never determined, it is just assumed that they are first-order in substrate. It is not unlikely that the kinetic dependence on the substrate changes during the reaction, making an accurate determination of s extremely difficult (see reference 16).
24 Generally s < 15 is insufficient for practical purposes, 15 < s < 30 is moderate to good and s > 30 is excellent; K. Faber, Biotransformations in Organic Chemistry, Springer, Berlin, 1992, p. 34.


30 Because of the relatively large error, especially for higher $s$ values, the $s$ values are just given to facilitate comparison between the different experiments.

31 The amount of organozinc reagent was chosen to be 0.8 equivalent to make sure that the reaction goes to over 50% conversion. No excess of zinc reagent was used to prevent the reaction from going to completion before enough data points have been gathered. The amount of zinc reagent that is used should in principle have no effect on the selectivity of the process.


36 The 1,4-addition on 2-cyclohexenone using 1 mol% Cu(OTf)$_2$, 2 mol% ($S,R,R$)-L1 and 1.5 equivalents of Et$_2$Zn in CH$_2$Cl$_2$ at $-30$ °C gives rise to the formation of ($S$)-3-ethylcyclohexanone in 92% ee. R. Naasz, unpublished results.

37 Note that this is a theoretical value, in contrast to the data given in the tables which are all actual data points.

38 Noyori et al. determined the relative initial rate of methylation vs. ethylation to be 1:90 for the 1,4-addition to 2-cyclohexenone using their catalytic system: M. Kitamura, T. Miki, K. Nakano, R. Noyori, *Bull. Chem. Soc. Jpn.* 2000, 73, 999. Experiences in our group show that the 1,4-addition of Me$_2$Zn using our standard conditions is very sluggish, often requiring overnight reaction to go to completion.

39 Unpublished results, see the forthcoming undergraduate report of R. Jagt, University of Groningen.


Copper-phosphoramidite catalyzed kinetic resolution of chiral 2-cyclohexenones

47 a) F. Bertozzi, P. Crotti, B. L. Feringa, F. Macchia, M. Pineschi, Synthesis 2001, 483; See also