Catalytic asymmetric conjugate additions and Heck reactions
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Chapter 2

Copper-catalysed conjugate additions to cyclohexadienones*

In this Chapter an overview will be given of our efforts on the copper phosphoramidite catalysed conjugate addition of dialkylzinc reagents to cyclohexadienones. These cyclohexadienones have hardly been investigated as substrates in asymmetric catalytic conversions. Two types of cyclohexadienones were studied; cyclohexadienone ketals and cyclohexadienone ethers. The latter substrates offer the interesting feature to introduce two stereocenters simultaneously in the product upon conjugate addition.

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2.1 Introduction

The conjugate addition of dialkylzinc reagents to cyclic enones catalysed by a copper-phosphoramidite complex was discussed, together with related matters, in the previous chapter. The chiral copper-L1 catalyst proved to be very efficient for a large number of substrates, and this system is now used in a number of asymmetric conjugate addition reactions. Typical examples include the synthesis of bicyclic compounds through annelation methodology or metathesis reactions, or the total synthesis of PGE1 methyl ester in only seven steps using a catalyst based on (S, R, R)-L1. Preliminary results on cyclohexadienones as substrates were reported as early as 1997, and in this chapter the results of further investigations using these very interesting substrates in the copper-L1 catalysed conjugate addition of dialkylzinc reagents will be discussed.

2.2 Cyclohexadienones as synthons

2,5-Cyclohexadienones are attractive substrates for conjugate additions as the chiral products may be subject to further 1,4-additions or might be employed in asymmetric cycloadditions. Due to their multifunctional nature (alkene, enone, ketone and a ketal if R1=R2= OR), they are very versatile prochiral synthons. (See Figure 2.1) Their cyclic structure makes them even more interesting, since asymmetry (once introduced) can easily be transferred in other reactions on these compounds (asymmetric induction) due to the reduced conformational flexibility. Furthermore, this class of compounds has barely been explored in enantioselective catalysis and the highly symmetric nature offers a critical test for any chiral catalyst. Several elegant methods have been reported to obtain chiral synthons based on 4,4-disubstituted cyclohexadienones; most of these approaches involve the temporary conversion to tricyclic adducts which are obtained in optically active form, either by diastereoselective [4+2]-cycloaddition using a chiral cyclopentadiene derivative, via desymmetrisation of meso-tricyclic adducts with the aid of a lipase or other methods.
In the following sections two types of 4,4-disubstituted-2,5-cyclohexadienones will be studied. The first type being 4,4-dialkoxy-2,5-cyclohexadienones (type A) and the second (type B) being 4-alkyl-4-alkoxy-cyclohexadienones. For simplicity, these will be abbreviated as cyclohexadienone ketals and cyclohexadienone ethers, respectively. (see Figure 2.2) When spoken in general, cyclohexadienone will be used.

A conjugate addition to a cyclohexadienone containing at least one alkoxy substituent at the C-4 position results in the formation of a rather unstable enolate, which in the presence of H⁺ will eliminate ROH and give the phenol as a product (See Scheme 2.1). This aromatisation is so favourable that conjugate additions to cyclohexadienones have been used as a synthetic route to 3,4-disubstituted phenols. 7

Whereas nucleophilic 1,2-additions to cyclohexadienones are well studied, 8 conjugate addition reactions of, for example, alkyllithium reagents, 9 dimethyl malonate 10 and acyli-
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nickel complexes\textsuperscript{11} to cyclohexadienones have been reported, but none of these are catalytic or enantioselective.

\[
\begin{align*}
\text{R}_1 \text{OR}_2 & \quad \text{RM} \quad \rightarrow \quad \text{R}_1 \text{OR}_2 \\
\text{OM OH} & \quad \rightarrow \quad \text{OM} \\
\text{R} & \quad \rightarrow \quad \text{OH} \\
\text{R}_2 & \quad \rightarrow \quad \text{R}_2 \text{OH}
\end{align*}
\]

**Scheme 2.1** Conjugate addition followed by acidic work-up leads to 3-alkylated phenols.

A nice example of an intramolecular Michael-type conjugate addition was reported by Hart and coworkers.\textsuperscript{12} Cyclisation of a proline derived cyclohexadienone ether \textit{2.1} leads to perhydroindole \textit{2.2}, a model compound in the synthesis of several alkaloids. (See Scheme 2.2)

\[
\begin{align*}
\text{MeO} & \quad \rightarrow \quad \text{MeO} \\
\text{HN} & \quad \rightarrow \quad \text{N} \\
\text{OO} & \quad \rightarrow \quad \text{N}
\end{align*}
\]

**Scheme 2.2** Proline-based cyclohexadienone \textit{2.1} used to obtain perhydroindole \textit{2.2}: a model compound in the synthesis of several alkaloids.\textsuperscript{12}

To our knowledge the only catalytic enantioselective conjugate addition to cyclohexadienones was reported by Iwata et al.,\textsuperscript{13} who described a Cu-catalysed addition of trimethylaluminum to \textit{2.3} to afford 3,4,4,5-tetramethylcyclohex-2-enone \textit{2.4} with ee’s up to 68%. They were able to extend this catalytic reaction to the synthesis of (-)-solavetivone,\textsuperscript{14} a phytoalexin found in \textit{e.g.} air-dried tobacco leaves\textsuperscript{15} (see Scheme 2.3)

\[
\begin{align*}
\text{Me}_3\text{Al} & \quad \text{CuOTf (5 mol\%)} \\
\text{TBDMSOTf} & \quad \text{THF 0\textdegree C} \\
\text{OMe} & \quad \rightarrow \quad \text{OMe} \\
\text{MeO} & \quad \rightarrow \quad \text{MeO} \\
\text{N} & \quad \rightarrow \quad \text{N}
\end{align*}
\]

**Scheme 2.3** Copper-catalysed asymmetric conjugate addition of Me\textsubscript{3}Al to cyclohexadienone \textit{2.3} and structure of (-)-solavetivone.\textsuperscript{13,14}


2.4 Selectivity in conjugate additions

Conjugate addition to symmetric cyclohexadienones results in desymmetrisation of the prochiral dienone moiety (Scheme 2.4). Side selective addition affords a single stereocenter in case the 4,4-substituents are equal i.e. Re versus Si-face attack of the organometallic reagent (side selectivity; Scheme 2.4a). If the substituents at the 4-position are different, Si or Re-face selective attack gives rise to the formation of two stereocenters in a single step (side and face selectivity; Scheme 2.4b). Will the chiral catalyst based on L1 be able to distinguish Re/Si faces and pro-R/pro-S positions in these highly symmetric cyclohexadienones? Since these cyclohexadienones can be easily prepared in one step from the corresponding phenols\textsuperscript{10,16} (vide infra) this represents an attractive route to chiral multifunctional synthons in just two steps from phenols. (See Scheme 2.4)

Scheme 2.4 Depending on the substituents, conjugate addition to cyclohexadienones might provide a way to obtain cyclic enones containing one (path a) or two (path b) stereocenters in just two steps, starting from phenols.

Face selectivity in conjugate additions to cyclohexadienones has been observed previously: Liotta et al\textsuperscript{17} described conjugate additions of RMgBr reagents to 4-hydroxy-4-alkyl substituted cyclohexadienones and found a cis-directing effect, which was ascribed to chelating of the hydroxy group to the organometallic reagent (See Scheme 2.5).

Scheme 2.5 Face selectivity in the conjugate addition.\textsuperscript{17}
Diastereoselectivity studies in conjugate addition of organoaluminum reagents to (R)-[(p-tolylsulfinyl)methyl]quinols were reported by Carmen Carreño et al., who observed the formation of the product as a single diastereoisomer.\textsuperscript{18} The hydroxy group provides anchimeric assistance in the transfer of the reagent. When organocuprates were employed as organometallic reagents, the reaction was extremely sluggish.

A cis-directing effect of the methoxy-substituent in the organoaluminum mediated conjugate addition of RLi and RMgBr to cyclohexadienone ethers has been observed by Swenton et al.\textsuperscript{9} (see Scheme 2.6) This indicates that the copper-catalysed conjugate addition of dialkylzinc reagents might also benefit from the chelating properties of the alkoxy moiety present in the cyclohexadienones.

\textbf{Scheme 2.6 }Cis directing effect of the alkoxy moiety.\textsuperscript{9}

\section*{2.5 Synthesis of cyclohexadienones}

The synthesis of cyclohexadienone dimethoxyketal (2.11) has been described previously, and involves anodic oxidation of 1,4-dimethoxybenzene (2.9) to 1,1,4,4-tetramethoxy cyclohexadienone\textsuperscript{19} (2.10), followed by acid catalysed mono hydrolysis\textsuperscript{19,20} (see Scheme 2.7). Although the electrochemical oxidation proceeded smoothly and the product could be isolated in >90\% yield, the hydrolysis of only one ketal moiety was very difficult. In our hands, selective mono hydrolysis was seldom achieved, and in general p-benzoquinone was obtained as the main product together with only small quantities of the desired ketal 2.11.

\textbf{Scheme 2.7} Synthesis of cyclohexadienone 2.11 by electrochemical oxidation of 2.9 followed by selective hydrolysis.

Several studies have shown that a variety of oxidising agents is capable of converting p-methoxyphenols to quinone monoketals.\textsuperscript{21} However, these reactions usually require long reaction times, harsh conditions and result often in complex reaction mixtures. More recently,
Pellet et al. developed a very efficient oxidation based on hypervalent iodine compounds, leading to several cyclohexadienone ketals or cyclohexadienone ethers. The conditions for this reaction are very mild: the 4-substituted phenol is dissolved in the corresponding alcohol (which is the nucleophile) and a solution of phenyliododiacetate (PIDA) in the alcohol is added dropwise at ambient temperature over a period of 30 min. After this period the reaction is complete. The reactions usually yield only a single product and typical isolated yields are 60-90%.

We synthesised a number of cyclohexadienone derivatives according to this method. Purification by column chromatography (SiO₂, Hex/EtOAc) yielded the products as yellow oils. Starting from 4-methoxyphenol the cyclohexadienone dimethoxy-monoacetal was obtained in 88% yield, whereas the ethyl and n-propyl analogues and were formed in 85% and 33% yield, respectively. Monoethers and were easily obtained in 73% and 60% yield, respectively. Mixed ketal was formed in 94% yield (Scheme 2.8).

![Scheme 2.8](image)

**Scheme 2.8** Oxidation of 4-substituted phenols using PIDA as the oxidant, leading to cyclohexadienones and.

Bicyclic monoether was obtained by phenolic oxidation of in 40% yield, using the stronger oxidant PIFA (phenyliododi(trifluoroacetate)) in the presence of acetonitrile as solvent. (See Scheme 2.9)

![Scheme 2.9](image)

**Scheme 2.9** Intramolecular oxidation of 2.23, using PIFA.
The size and flexibility of the ketal moiety will probably have a profound effect on selectivity and reactivity in the asymmetric conjugate addition reaction. Therefore, some cyclohexadienone ketal were synthesised starting from dienone 2.11, through BF₃-promoted trans acetalisation.²⁴ (See Scheme 2.10) We were unable to achieve transacetalisation using tBuOH, PhOH or PhCH₂OH or diols like cresol or pinacol via this method, however the synthesis of 2.25-2.27 was successful. The products were obtained as yellow oils in good yields of 75%, 68% and 78%, respectively.

![Scheme 2.10 Transacetalisation using BF₃.Et₂O.](image)

All cyclohexadienones obtained were surprisingly stable towards hydrolysis. They could be stored under normal atmosphere and purified by column chromatography on SiO₂. After two months the cyclohexadienones had changed color from yellow to brown, but by ¹H NMR no contamination could be detected. Simple bulb-to-bulb distillation or quick column chromatography afforded the cyclohexadienones again as yellow oils.

2.6 Catalytic asymmetric copper-catalysed conjugate additions to cyclohexadienones

The conjugate additions of dialkylzinc reagents to cyclohexadienones were performed using the optimised conditions for cyclic enones. (see Scheme 2.11) The reaction was performed under an Ar atmosphere in toluene on a 1 mmol scale, using 2 mol% of an in situ preformed catalyst from Cu(OTf)₂ and the chiral ligand. One mmol of substrate was added and the mixture was cooled to −25 °C, after which 1.5 equiv. of Et₂Zn in toluene (1.1 M) was added. The mixture was stirred for 16 h at this temperature, then quenched with 1N NaOH, extracted with EtOAc and purified by column chromatography.

![Scheme 2.11 Standard conditions for the conjugate addition of Et₂Zn to cyclohexadienones.](image)
2.6.1 Conjugate additions to cyclohexadienone ketals 2.11, 2.18, 2.19 and 2.25-2.27

The conjugate addition of dialkylzinc reagents to cyclohexadienones turned out to be slower than the conjugate additions to the cyclic enones reported previously by our group. Usually reaction times of 16 h were necessary for full conversion. The reactions were clean and no 1,2-adduct was detected. Work-up had to be performed fast and under alkaline conditions, since the enolate that is formed during the reaction readily gives rise to the formation of the corresponding phenol. The formation of the phenol cannot be completely prevented in this way, even if work-up was performed at 0 °C. Usually 5-10% of phenol is formed, decreasing the isolated yield of the product.

The conjugate addition of Et₂Zn to cyclohexadienone monoketals with R₁ = R₂ (2.11, 2.18, 2.19 and 2.25-2.27) proceeded with high enantioselectivity (Table 2.1): for instance 3-ethyl-4,4-dimethoxy-cyclohexenone (2.28) with an ee of 98% was isolated. When the methoxy-substituents were replaced by the larger ethoxy groups the ee of the enone 2.29 dropped to 92% probably as a result of some steric interference. Unfortunately, we were not able to get satisfactory enantioseparation for the n-propyl derivative 2.30 on any of the chiral GC columns present in our laboratories.

Table 2.1 Conjugate additions to cyclohexadienone monoketals containing symmetric ketal moieties.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Dienone</th>
<th>R</th>
<th>1,4-adduct</th>
<th>Yield</th>
<th>E.e.</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.11</td>
<td>Et</td>
<td>2.28</td>
<td>65</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td>2.18</td>
<td>Et</td>
<td>2.29</td>
<td>59</td>
<td>92</td>
</tr>
<tr>
<td>3</td>
<td>2.19</td>
<td>Et</td>
<td>2.30</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
<tr>
<td>4</td>
<td>2.25</td>
<td>Et</td>
<td>2.31</td>
<td>68</td>
<td>92</td>
</tr>
<tr>
<td>5</td>
<td>2.26</td>
<td>Et</td>
<td>2.32</td>
<td>62</td>
<td>89</td>
</tr>
<tr>
<td>6</td>
<td>2.27</td>
<td>Et</td>
<td>2.33</td>
<td>75</td>
<td>85</td>
</tr>
<tr>
<td>7</td>
<td>2.11</td>
<td>Me</td>
<td>2.34</td>
<td>76</td>
<td>99</td>
</tr>
</tbody>
</table>

a isolated yield b determined by chiral GC c not determined

When cyclic ketals were used, an interesting decrease of the ee was observed from 92% to 85% by increase of ring size and bulk of the substituents (Table 2.1, entries 4-7, adducts 2.31-2.33). Cyclohexadienone-ethylene glycol ketal (2.25) gave a slightly lower enantioselectivity in the 1,4-addition compared to dimethoxy analogue 2.11 (92 vs. 98% ee). Probably this is due to the rigidity of the ethylene glycol acetal, and not the result of a difference in size. Conjugate addition of Me₂Zn to cyclohexadienone 2.11 affords the 1,4-adduct 2.34 with a rewarding 99% enantiomeric excess.

2.6.2 Conjugate additions to cyclohexadienone ethers and cyclohexadienone ketal 2.37.

Since the ketal moiety might coordinate to the chiral Cu-catalyst, it is interesting to know what the stereochemical result of the conjugate addition of Et₂Zn would be in the case of 4,4-
disubstituted cyclohexadienones with only one alkoxy-moiety attached to the cyclohexadienone. The introduction of two different substituents at C-4 will give rise to the formation of two stereogenic centers as depicted in Scheme 2.4. It is interesting to investigate if this substitution pattern leads to high diastereoselectivity and enantioselectivity for both diastereoisomers and if the stereoselectivity only depends on the size of the C-4 substituents. The 1,4-addition of Et₂Zn to substrate 2.21 reveals that the product 2.36 is formed as a mixture of two diastereoisomers. The diastereomeric ratio was, however, 9/1. Unfortunately, we were not able to separate the racemic mixture on any chiral GC column present in our lab, but after reduction of the remaining alkene, enantioseparation was achieved. The ee’s of the major and minor product are 97% and 85%, respectively (see Table 2.2).

### Table 2.2 Conjugate addition of Et₂Zn to cyclohexadienone ethers and 2.37 using a catalyst prepared from S,R,R L₁ and Cu(OTf)₂

<table>
<thead>
<tr>
<th>Entry</th>
<th>Dienone</th>
<th>R¹</th>
<th>R²</th>
<th>1,4-adduct</th>
<th>Dr (cis/trans)ᵃ</th>
<th>Yield (%)ᵇ</th>
<th>Ee major (%)ᶜ</th>
<th>Ee minor (%)ᶜ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.20</td>
<td>Me</td>
<td>OMe</td>
<td>2.35</td>
<td>90/10</td>
<td>60</td>
<td>97ᵈ</td>
<td>85ᵈ</td>
</tr>
<tr>
<td>2</td>
<td>2.21</td>
<td>CH₂Ph</td>
<td>OMe</td>
<td>2.36</td>
<td>97/3</td>
<td>53</td>
<td>93ᵈ</td>
<td>n.d.ᵉ</td>
</tr>
<tr>
<td>3</td>
<td>2.22</td>
<td>OCH₂Ph</td>
<td>OMe</td>
<td>2.37</td>
<td>1/1</td>
<td>58</td>
<td>98</td>
<td>98</td>
</tr>
<tr>
<td>4</td>
<td>2.24</td>
<td>-CH₂CH₂CH₂O-</td>
<td></td>
<td>2.38</td>
<td>99/1</td>
<td>66</td>
<td>65</td>
<td>n.d.ᵉ</td>
</tr>
</tbody>
</table>

ᵃ Determined by ¹H NMR ᵇ Combined isolated yield (minor + major isomer) ᵇ determined by chiral GC ᵈ enantioseparation was achieved after hydrogenation of the remaining alkene. ᵉ not determined.

In the case of cyclohexadienone ketal 2.21 containing a methoxy-substituent and a substantially larger benzyl group, nearly one diastereoisomer of adduct 2.36 is observed (dr 97/3) with an ee of 93% for the major diastereoisomer. Again, enantioseparation by GC or HPLC was only possible after reduction of the alkene. When the alkoxy and alkyl substituent are linked as in cyclohexadienone 2.24, a high diastereoselectivity (dr 99/1) in the formation of adduct 2.38 is observed. The ee of the major diastereoisomer was, however, only 65%. NOESY experiments indicated that in the cyclohexenones 2.35, 2.36 and 2.38 the ethyl substituent was introduced cis to the alkoxy group in the major isomer.²⁵

The origin of the observed diastereoselectivity could be a steric effect or chelation of the oxygen of the alkoxy moiety to the copper complex. The conjugate addition of diethylzinc was therefore performed with cyclohexadienone ketal 2.22, which contains two alkoxy-
substituents of different size. Adduct 2.37 was obtained as a 1 to 1 mixture of the two possible diastereoisomers, but much to our delight both isomers were nearly enantiomerically pure (ee 98%). It is therefore likely that the oxygen of the acetal or alkoxy-substituent interacts with the metal complex and therefore exerts a directing effect on the activated organometallic species in the copper catalysed enantioselective conjugate addition of dialkylzinc reagents to cyclohexadienones.

2.7 Miscellaneous approaches

The Diels-Alder reaction of 2.11 and 1-methoxybutadiene resulting in 2.39 is known to proceed smoothly and highly selectively.26 We wondered if a Diels-Alder reaction of 2.34 (ee 99%) to 2.40 would lead to a similar product, which contains four stereocenters. The hope was that the stereogenic center already present results in high asymmetric induction, leading to one regioisomer with a high optical purity. Unfortunately, the Diels Alder reaction did not proceed. Even after two days of refluxing in toluene, only starting material was recovered. Apparently, the double bond is no longer a reactive dienophile, or there is too much steric hinderance from the methyl substituent.

![Diagram of attempted Diels-Alder reaction of methoxybutadiene and 2.34.](image)

**Scheme 2.12** Attempted Diels-Alder reaction of methoxybutadiene and 2.34.

In the conjugate addition of dialkylzinc reagents to cyclohexenones, it is possible to trap the formed Zn-enolate *in situ* with e.g. an alkylbromide or an aldehyde. This trapping proceeds mainly *trans*- selective, creating a second stereocenter (or two additional stereocenters when an aldehyde is used as the trapping agent). Unfortunately, the Zn-enolate formed in the conjugate addition to cyclohexadienone 2.11 apparently was unreactive, since less then 5% of
product was formed after addition of 1.2 equiv. of aldehyde, even after 2 days at ambient temperature.

Scheme 2.13 Attempted tandem addition of the in situ formed Zn-enolate to benzaldehyde.

2.8 Conclusions

In conclusion, the copper-phosphoramidite chiral catalyst, prepared from Cu(OTf)₂ and L₁ shows remarkably high levels of stereoselectivity in the 1,4-addition to cyclohexadienones as ee’s up to 99% were observed. A remarkable diastereoselectivity was observed for the cyclohexadienone monoethers, where the main product obtained was the cis-isomer (with respect to the alkoxy moiety). This indicates that in the catalytically active complex, the alkoxy group is probably involved in coordination to the copper-species, thus generating the cis-adduct. Based on this finding a new catalytic method was developed to prepare several multifunctional cyclohexenones with high dr and high ee. These chiral multifunctional cyclohexenones can be subjected to a second catalytic asymmetric conjugate addition, which will be discussed in the following chapter.

2.9 Experimental section

General remarks:
All solvents were reagent grade and were dried and distilled, if necessary, following standard procedures. Reagents were purchased from Aldrich, Acros Chimica, Merck or Fluka and used as received unless stated otherwise. ¹H NMR and ¹³C NMR spectra were recorded on a Varian VXR-300 spectrometer (at 300 MHz and 75.4 MHz, respectively). Chemical shifts are reported in δ units (ppm) relative to the residual deuterated solvent signals of CHCl₃ (¹H: 7.24 ppm, ¹³C: 77.0 ppm). Optical rotations were measured at ambient temperature using a Perkin Elmer 241 polarimeter. Mass spectra were recorded on a AEI-MS-902 mass spectrometer by A. Kiewiet. GC measurements were performed on either a HP 5890 A, HP 5890 series II or a HP 6890 gas chromatograph using a flame ionisation detector. To ensure accurate determination of ee’s, racemic mixtures of all products were prepared employing the
copper-phosphoramidite catalysed conjugate addition with the use of 10 mol% of Cu(OTf)$_2$ and 20 mol% of racemic MonoPhos.$^{27}$

**Typical procedure for the oxidation of 4-substituted phenols to cyclohexadienones using PIDA as the oxidant.**
The phenol (10 mmol) was dissolved in 10 ml of the appropriate alcohol at ambient temperature and over a period of 30 min., a solution of 10 mmol of PIDA in the 20 ml of the alcohol was added. After 2 h, the mixture was diluted with water (100 ml) and extracted with diethylether (3x 100 ml). The combined organic layers were washed with 1N NaOH, brine, and dried on Na$_2$SO$_4$. Filtration and concentration yields a yellow oil was purified by column chromatography (SiO$_2$, Hex/EtOAc = 8/1)

**Typical procedure for the transacetalisation of 2.11 to cyclic acetals 2.25-2.27.**
To a solution of 1.5 g 2.11 (10 mmol) and 100 mmol of diol in 50 ml of Et$_2$O at 0°C, was added slowly a solution of 20 mmol BF$_3$.Et$_2$O in 50 ml of Et$_2$O. The mixture was stirred at 0°C for 1 h, after which 1N aq. NaOH (100 ml) was added. The mixture was extracted with ether (2x 50 ml), the combined organic layers were washed with brine, dried on Na$_2$SO$_4$, filtered and the solvent evaporated in vacuo, yielding a brown oil. The crude product was purified by column chromatography (SiO$_2$, Hex/EtOAc = 8/1).

**General procedure for 1,4-addition of dialkylzinc reagents to cyclohexadienones.**
Under Argon, a solution of Cu(OTf)$_2$ (9.0 mg, 0.024 mmol) and (S, R, R) L1 (26 mg, 0.048 mmol) in 5.0 ml of toluene was stirred for 1 h at rt. The colourless solution was cooled to -25°C and 1.0 mmol of dienone and 1.5 ml of R$_2$Zn (1.1 M in toluene) were added. After 16 h, the reaction mixture was quenched with 1N NaOH (5.0 ml) and then extracted with Et$_2$O (3x 20 ml). The combined organic layers were extracted with 1.0 N aq. NaOH (30 ml), washed with brine (30 ml), dried on Na$_2$SO$_4$ and the solvents were evaporated. Column chromatography (SiO$_2$ (hexane/EtOAc, 5/1)) yielded the pure 1,4-adduct. Yields and e.e.’s are given in Table 2.1 and Table 2.2.

### 4,4-Dimethoxycyclohexa-2,5-dienone (2.11)$^{28}$
Starting from 2.0 g (16.0 mmol) 4-methoxyphenol and using MeOH as a solvent, this was obtained as a light yellow oil. 88% (2.10 g).

$^1$H NMR $\delta$ 3.31 (s, 6H), 6.24 (d, $J = 10$ Hz, 2H), 6.86 (d, $J = 10$ Hz, 2H). $^{13}$C NMR $\delta$ 50.4 (q), 91.9 (s), 129.9 (d), 143.6 (d), 185.2 (s). HRMS found 154.062, calc. for C$_8$H$_{10}$O$_3$ 154.063.

### 4,4-Diethoxycyclohexa-2,5-dienone (2.18)
Starting from 3.2 g (23.0 mmol) 4-ethoxyphenol using EtOH as a solvent 2.18 was obtained as a yellow oil in 85 % (3.5 g).

$^1$H NMR $\delta$ 1.17 (t, $J = 8$ Hz, 6H), 3.57 (q, $J = 8$ Hz, 4H), 6.21 (d, $J = 10$ Hz,
2H), 6.82 (d, J = 10 Hz, 2H). $^{13}$C NMR δ 15.26 (q), 58.18 (t), 92.81 (s), 129.35 (d), 144.25 (d), 185.18 (s). HRMS calcd for C_{10}H_{14}O_{3} 182.094, found 182.094.

4,4-Di-\textit{n}-propoxycyclohexa-2,5-dienone (2.19)

Starting from 2.0 g (13.2 mmol) 4-propoxyphenol using \textit{n}-Propanol/CH_{3}CN (1/1) as a solvent this was obtained as a yellow oil in 33% (0.91 g).

$^{1}$H NMR δ 0.89 (t, J = 8 Hz, 6 H), 1.59 (s, J = 8 Hz, 4H), 3.49 (t, J = 8 Hz, 4H), 6.22 (d, J = 11 Hz, 2H), 6.81 (d, J = 11 Hz, 2H). $^{13}$C NMR δ 10.21 (q), 22.34 (t), 64.26 (t), 92.16 (s), 129.24 (d), 144.39 (d), 185.48 (s). HRMS calcd for C_{12}H_{18}O_{3} 210.125, found 210.123.

4-Methyl-4-methoxycyclohexa-2,5-dienone (2.20)

Starting from 3.0 g (27.7 mmol) p-methylphenol and using MeOH as a solvent the product was obtained as yellow crystals (m.p. 65-68°C) (73%, 2.8 g).

$^{1}$H NMR δ 1.36 (s, 3H), 3.14 (s, 3H), 6.24 (d, J = 10 Hz, 2H), 6.70 (d, J = 10 Hz, 2H). $^{13}$C NMR δ 26.28 (q), 53.21 (q), 72.63 (s), 130.47 (d), 151.66 (d), 185.08 (s).

HRMS calcd. for C_{8}H_{10}O_{2} 138.068, found 138.067.

4-Benzyl-4-methoxy-2,5-cyclohexadienone (2.21)

Starting from (1.97 g, 10.4 mmol) 4-benzylphenol and using MeOH as a solvent, 2.21 was obtained in 60% (1.33 g) as a yellow oil.

$^{1}$H NMR δ 2.99 (s, 2H), 3.21 (s, 3H), 6.29 (d, J = 10 Hz, 2H), 6.73 (d, J = 10 Hz, 2H). $^{13}$C NMR 44.0 (t), 49.7 (q), 74.8 (s), 125.7 (d), 127.9 (d), 128.4 (d), 132.4 (d), 140.2 (s), 152.0 (d), 187.0 (s). HRMS calcd. for C_{14}H_{14}O_{2} 214.099, found 214.100.

4-Methoxy-4-benzyloxycyclohexa-2,5-dienone (2.22)

Starting from 5 mmol (1.0 g) of p-benzyloxyphenol and using MeOH as a solvent 2.22 was obtained as a yellow oil (1.08 g, 94%).

$^{1}$H NMR δ 3.36 (s, 3H), 4.6 (s, 2H), 6.23 (d, J = 10 Hz, 2H), 6.85 (d, J = 10 Hz, 2H), 7.27 (m, 5H). $^{13}$C NMR δ 50.51 (q), 64.82 (t), 92.60 (s), 127.46 (d), 127.79 (d), 128.40 (d), 137.42 (s), 143.34 (d), 185.08 (s).

HRMS calcd. for C_{14}H_{14}O_{3} 230.094, found 230.094.

1-Oxaspiro[4,5]deca-6,9-dien-8-one (2.24)

To a stirred solution of 1.52 g (10 mmol) of 3-(4-hydroxyphenol)-propanol 2.23 and 3 ml of pyridine in 40 ml of CH_{3}CN at 0°C, a solution of 0.43 g (10 mmol) PIFA in 20 ml CH_{3}CN was added. The mixture was stirred for 30 min at ambient temperature, diluted with 100 ml of water and extracted with ether (3x 50 ml). The combined organic layers were washed with brine, dried over MgSO_{4}, and concentrated in vacuo. The residue was purified by column chromatography (SiO_{2}, hexane:EtOAc = 3:2) to yield 0.30 g (40%) of pure monoether 2.24 as a colorless oil.
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$^1$H NMR $\delta$ 2.10 (m, 4H), 4.08 (m, 2H), 6.13 (d, $J = 10$ Hz, 2H), 6.80 (d, $J = 10$ Hz, 2H). $^{13}$C NMR 25.3 (t), 35.7 (t), 67.8 (t), 75.9 (s), 125.7 (d), 148.2 (d), 184.3 (s). HRMS calcd. for C$_9$H$_{10}$O$_2$ 150.068, found 150.067.

1,4-Dioxa-spiro[4.5]deca-6,9-dien-8-one (2.25)
Starting from 2.0 g (13.0 mmol) of 2.11, and using ethyleneglycol as the diol, the product was obtained in 75% (1.45 g) as a yellow oil.

$^1$H NMR $\delta$ 3.37 (s, 4H), 6.14 (d, $J = 10$ Hz, 2H), 6.78 (d, $J = 10$ Hz, 2H). $^{13}$C NMR $\delta$ 65.64 (t), 98.01 (s), 128.82 (d), 143.11 (d), 185.67 (s). HRMS calcd. for C$_8$H$_8$O$_3$ 152.047, found 152.048.

1,5-Dioxa-spiro[5.5]undeca-7,10-dien-9-one (2.26)
Starting from 2.0 g (13.0 mmol) of 2.11, and using 1,3-dihydroxypropane as the diol, this was isolated in 68% (1.45 g) as a colourless oil.

$^1$H NMR $\delta$ 1.93 (q, $J = 5$ Hz, 2H), 4.09 (t, $J = 5$ Hz, 4H), 6.15 (d, $J = 10$ Hz, 2H), 7.19 (d, $J = 10$ Hz, 2H). $^{13}$C NMR $\delta$ 24.68 (t), 60.71 (t), 88.69 (s), 128.26 (d), 141.75 (d), 185.95 (s). HRMS calcd. for C$_9$H$_{10}$O$_3$ 166.065, found 166.063.

3,3-Dimethyl-1,5-dioxa-spiro[5.5]undeca-7,10-dien-9-one (2.27)
Starting from 2.0 g (13.0 mmol) of 2.11, and using 1,3-dihydroxy-2,2-dimethylpropane as the diol the product 2.27 was isolated in 78% (1.98 g) as a yellow oil.

$^1$H NMR $\delta$ 1.04 (s, 6H), 3.67 (s, 4H), 6.14 (d, $J = 10$ Hz, 2H), 7.14 (d, $J = 10$ Hz, 2H). $^{13}$C NMR $\delta$ 22.36 (q), 29.85 (s), 71.67 (t), 88.49 (s), 128.36 (d), 141.41 (d), 184.80 (s). HRMS calcd. for C$_{11}$H$_{14}$O$_3$ 194.094, found 194.093.

5-Ethyl-4,4-dimethoxy-2-cyclohexenone (2.28)

$^1$H NMR $\delta$ 0.80 (t, 3H), 1.03 (m, 1H), 1.49 (m, 1H), 2.11 (m, 1H), 2.38 (m, 1H), 2.66 (m, 1H), 3.13 (s, 3H), 3.16 (s, 3H), 5.88 (d, $J = 10.3$ Hz, 1H), 6.56 (dd, $J = 10.3$ and 1.5 Hz, 1H). $^{13}$C NMR $\delta$ 9.34, 18.55, 35.82, 40.20, 45.23, 47.18, 96.54, 128.39, 144.55, 196.54. HRMS calcd. for C$_{10}$H$_{16}$O$_3$ 184.110, found 184.108, E.e. determination: GC CP-Cyclodex-B, 115 °C, rt (min) 18.1, 18.4.

5-Ethyl-4,4-diethoxy-2-cyclohexenone (2.29)

$^1$H NMR $\delta$ 0.95 (t, 3H), 1.15 (t, 6H), 2.13 (m, 1H), 2.45 (m, 1H), 2.86 (m, 1H), 3.53 (m, 4H), 5.94 (d, $J = 9.4$ Hz, 1H), 6.71 (d, $J = 9.4$ Hz, 1H). $^{13}$C NMR $\delta$ 11.62, 14.91, 15.22, 20.74, 38.29, 43.30, 66.19, 57.32, 98.59, 130.23, 148.00, 199.39. HRMS calcd. for C$_{12}$H$_{20}$O$_3$ 212.141, found 212.142, E.e. determination: GC CP-Cyclodex-B column, 125°C, rt (min) 51.9, 52.8.
10-Ethyl-1,4-dioxaspiro[4,5]dec-6-en-8-one (2.31)

\[
\begin{align*}
\text{H NMR } & \delta 0.95 \text{ (t, 3H), 1.13 (m, 1H), 1.76 (m, 1H), 2.19 (m, 1H), 2.45 (m, 1H), 2.77 (m, 1H), 3.93 (m, 4H), 5.95 (d, } J = 9.6 \text{ Hz, 1H), 6.59 (d, } J = 9.6 \text{ Hz, 1H).} \\
\text{C NMR } & \delta 11.11, 20.61, 39.64, 44.31, 65.42, 65.49, 105.87, 129.44, 146.60, 199.15. \text{ HRMS calc. for C}_{10}H_{14}O_3 182.094, \text{ found 182.096.}
\end{align*}
\]
E.e. determination: GC GTA column, 140°C, rt (min) 43.5, 46.1.

11-Ethyl-1,5-dioxaspiro[5,5]undec-7-en-9-one (2.32)

\[
\begin{align*}
\text{H NMR } & \delta 0.88 \text{ (t, 3H), 1.15 (m, 1H), 1.56 (m, 1H), 2.12 (m, 3H), 2.56 (m, 2H), 4.01 (m, 4H), 6.00 (d, } J = 10 \text{ Hz, 1H), 7.35 (d, } J = 10 \text{ Hz, 1H).} \\
\text{C NMR } & \delta 11.48, 20.32, 25.07, 38.32, 45.60, 60.24, 60.47, 95.47, 129.75, 143.86, 199.38. \text{ HRMS calcd. for C}_{11}H_{16}O_3 196.110, \text{ found 196.108.}
\end{align*}
\]
E.e. determination: GC GTA column, 160°C, rt (min) 31.2, 32.9.

11-Ethyl-3,3-dimethyl-1,5-dioxaspiro[5,5]undec-7-en-9-one (2.33)

\[
\begin{align*}
\text{H NMR } & \delta 0.82 \text{ (s, 3H), 0.95 (t, 3H), 1.13 (s, 3H), 1.32 (m, 1H), 2.08 (m, 2H), 2.48 (m, 3H), 3.40-3.98 (m, 4H), 6.01 (d, } J = 11 \text{ Hz, 1H), 7.26 (d, } J = 11 \text{ Hz, 1H).} \\
\text{C NMR } & \delta 11.36, 20.18, 21.96, 22.62, 29.84, 38.35, 45.69, 60.23, 70.75, 70.99, 95.27, 129.93, 143.52, 199.41. \text{ HRMS calc. for C}_{13}H_{20}O_3 224.141, \text{ found 224.137.}
\end{align*}
\]
E.e. determination: GC CP-cyclodex-B column, 140 °C, rt (min), 110, 112.

5-Methyl-4,4-dimethoxy-2-cyclohexenone (2.34)

\[
\begin{align*}
\text{H NMR } & \delta 0.95 \text{ (d, } J = 7.1 \text{ Hz, 3H), 2.20 (d, } J = 7 \text{ Hz, 1 H), 2.58, (m, 1 H), 2.88 (d, } J = 7 \text{ Hz, 1H), 3.23 (d, } J = 3 \text{ Hz, 6 H), 6.01 (d, } J = 10.6 \text{ Hz, 1H), 6.65 (d, } J = 10.6 \text{ Hz, 1H).} \\
\text{C NMR } & \delta 14.64, 35.28, 42.01, 47.4, 49.59, 99.02, 130.48, 146.45, 198.93. \text{ HRMS calc for C}_{9}H_{14}O_3 170.094, \text{ found 170.096.}
\end{align*}
\]
E.e. determination: GC GTA column, 150°C, rt (min), 15.5, 16.3.

\textit{Cis}-5-ethyl-4-methyl-4-methoxy-2-cyclohexenone (2.35)

\[
\begin{align*}
\text{H NMR } & \delta 0.91 \text{ (t, } J = 7 \text{ Hz, 3H), 1.28 (m, 1H), 1.42 (s, 3H), 1.76 (m, 1H), 1.90 (m, 1H), 2.50 (m, 2H), 3.26 (s, 3H), 5.99 (d, } J = 10 \text{ Hz, 1H), 6.77 (d, } J = 10 \text{ Hz, 1H).} \\
\text{C NMR } & \delta 11.64, 20.80, 22.26, 38.28, 45.69, 50.24, 73.09, 129.41, 152.87, 199.78. \text{ HRMS calc. for C}_{10}H_{16}O_2 168.115, \text{ found 168.119.}
\end{align*}
\]
No e.e. determination method could be developed for this compound. However, the e.e. of the hydrogenated product \textit{Cis}-5-ethyl-4-methyl-4-methoxy-2-cyclohexenone (2.35a) could be determined.

\textit{Cis}-3-ethyl-4-methyl-4-methoxy-cyclohexanone (2.35a)

A spatula of Pd/C was added to a stirred solution of 0.3 mmol (58 mg) of 2.35 in 10 ml of CH₂Cl₂ and the flask was connected to a balloon filled with H₂. After 16 h the reaction mixture was filtered over Celite and the solvent evaporated after which pure 2.35a was obtained in 95% (48 mg) as a yellow
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oil.

$^1H$ NMR $\delta$ 0.85 (t, 3H), 1.23 (s, 3H), 1.58 (m, 4H), 2.30 (m, 5H), 3.23 (s, 3H). $^{13}C$ NMR $\delta$ 11.52, 21.26, 21.85, 33.23, 36.95, 41.26, 48.77, 73.50. HRMS calcd. for C$_{10}$H$_{18}$O$_2$ 170.130, found 170.132.

E.e. determination: GC Cp Cyclodex B column, T= 120 °C, rt (min.) 44.8, 45.3, 46.4, 48.3.

Cis-4-benzyl-5-ethyl-4-methoxy-2-cyclohexenone (2.36)

A small amount (15 mg) of pure cis-2.36 was isolated from its diastereoisomer by column chromatography. This was analysed by NMR and HRMS.

$^1H$ NMR $\delta$ 0.93 (t, 3H), 1.35 (m, 1H), 1.92 (m, 2H), 2.49 (m, 2H), 3.02 (d, $J$ = 14 Hz, 1H), 3.21 (d, $J$ = 14 Hz, 1H), 3.37 (s, 3H), 6.06 (d, $J$ = 10 Hz, 1H), 6.80 (d, $J$ = 10 Hz, 1H), 7.27 (m, 5H). $^{13}C$ NMR $\delta$ 11.52, 21.26, 29.61, 38.53, 41.53, 42.26, 51.27, 126.67, 128.23 (2x), 130.09 (2x), 130.95, 136.16, 150.94, 194.65. HRMS calcd. for C$_{16}$H$_{20}$O$_2$ 244.146, found 244.147.

No e.e. determination method could be developed for this compound. However, the e.e. of the hydrogenated product 2.36a could be determined.

Cis-4-benzyl-3-ethyl-4-methoxy-cyclohexanone (2.36a)

A spatula of Pd/C was added to a solution of 0.03 mmol (7.3 mg) ( of 2.36 was 10 ml of CH$_2$Cl$_2$ and the flask was connected to a balloon filled with H$_2$. After 16 h the reaction mixture was filtered over Celite and the solvent evaporated after which pure 2.36a was obtained. After 16 h the reaction mixture was filtered over Celite and the solvent evaporated after which pure 2.36a was obtained in 93% (6.9 mg) as a yellow oil.

$^1H$ NMR $\delta$ 0.89 (t, 3H), 1.39 (m, 1H), 1.60 (m, 2H), 2.02 (m, 1H), 2.19 (m, 2H), 2.35 (m, 2H), 2.45 (m, 1H), 3.03 (q, 2H), 3.39 (s, 3H), 7.23 (m, 5H). $^{13}C$ NMR $\delta$ 11.15, 22.46, 29.99, 36.65, 38.70, 41.26, 44.08, 126.44, 128.17, 130.10, 189.14. HRMS calcd. for C$_{16}$H$_{22}$O$_2$ 246.161, found 246.161.

E.e. determination: HPLC AS column, flow rate 1.5 ml/min, hexane/ipa: 90/10, rt (min) 6.9, 8.1.

Cis-4-benzylxyloxy-5-ethyl-4-methoxy-2-cyclohexenone (2.37)

$^1H$ NMR $\delta$ 0.87 (t, 3H), 1.1 (m, 1H), 1.72 (m, 1H), 2.1 (m, 1H), 2.52 (m, 1H), 2.81 (m, 1H), 3.27 (s, 3H), 4.50 (m, 2H), 5.98 (d, $J$ = 10 Hz, 1H), 6.72 (d, $J$ = 10 Hz, 1H), 7.25 (m, 5H). $^{13}C$ NMR $\delta$ 11.63, 20.95, 38.23, 43.08, 49.84, 64.40, 127.34, 127.62, 128.36, 130.85, 147.08, 196.54. HRMS calcd. for C$_{16}$H$_{23}$O$_2$ 248.177, found 248.177. E.e. determination: HPLC AS column, flow rate 2.0 ml/min, hexane/ipa: 80/20, rt (min) 11.3, 15.6.
Cis-10-ethyl-1-oxaspiro[4,5]dec-6-en-8-one (2.38)

\[1^1H \text{ NMR } \delta 0.86 (t, 3H), 1.23 (m, 1H), 1.69 (m, 1H), 1.85 (m, 2H), 1.98 (m, 2H), 2.13 (m, 1H), 2.48 (m, 2H), 3.91 (m, 2H), 5.82 (d, J = 10 Hz, 1H), 6.58 (d, J = 10 Hz, 1H). \]

\[13^1C \text{ NMR } \delta 11.87, 21.02, 26.06, 35.95, 39.64, 45.50, 68.33, 82.00, 127.40, 152.73, 199.14. \]

HRMS calcd. for C\textsubscript{11}H\textsubscript{16}O\textsubscript{2} 180.113, found 180.110.

E.e. determination: HPLC AS column, flow rate 1.5 ml/min, hexane/ipa:95/5, rt (min) 6.2, 7.4, 9.9, 15.1.

2.10 References


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22 (a) ref 16a (b) for a review on phenolic oxidations see: Pelter, A.; Ward, R. S. Tetrahedron 2001, 57, 273.


24 The trans acetalisation was performed using a similar method as reported by Pirrung and Nunn: Pirrung, M. C.; Nunn, D. S. Tetrahedron Lett. 1992, 33, 6591.

25 A cis-directing effect of the methoxy-substituent in the organoaluminum mediated conjugate addition of RLi and RMgBr to quinol ethers has been observed, see ref 8a.


