Novel Chiral Monodentate BINOL and TADDOL Derived Phosphorus Amidites; Synthesis and Application in the Copper(II) Catalyzed Conjugate Addition of Et₂Zn Reagents to Cyclic Enones and Benzalmalonates

7.1 Abstract

In this chapter the conjugate addition of diethylzinc to α,β-unsaturated esters and the conjugate addition tandem aldol reaction with 2-cyclopentenone using BINOL and TADDOL derived phosphorus amidites is described. Enantioselectivities up to 40% for benzalmalonates, and up to 62% for cyclopentenone were achieved. Remarkable enhancement of enantioselectivity was observed upon the addition of powdered molecular sieves to the reaction mixture.

7.2 Introduction

Conjugate addition reactions of carbon nucleophiles to α,β-unsaturated compounds are among the most widely used methods for carbon-carbon bond formation in organic synthesis. For this purpose several chiral organocopper compounds of the composition RCu(L*)Li have been applied to control the stereochemical outcome of the transfer of R to enone 7.1 (Scheme 7.1). In some cases enantioselectivities exceeded 90%. For example, the stoichiometric enantioselective addition of a chiral alkoxydimethylcuprate has been successfully applied in the synthesis of (R)-muscone (7.2, R=Me, n=10) with complete stereocontrol (Scheme 7.1). Several crucial problems were encountered however. First of all organocopper reagents show dynamic behavior in solution with equilibria between several species, which can lead to undesired competing reactions and decrease in enantioselectivity. Furthermore many of these chiral organocopper reagents show high substrate specificity and only give good enantioselectivities with one or a few substrates.

![Scheme 7.1 Stoichiometric enantioselective conjugate addition of organocopper reagents.](image)

Part of this work was published previously: Keller, E., Maurer, J., Naasz, R., Schrader, T., Meetsma, A., Feringa, B.L. Tetrahedron Asymm. 1998, 9, 2409.


Chapter 7

The problems encountered in these stoichiometric enantioselective conjugate additions may be solved by taking advance of the concept of ligand accelerated catalysis. The presence of a suitable chiral ligand can lead to the formation of a highly reactive and selective catalyst via self assembly. Lippard and co-workers were the first to report an enantioselective conjugate addition using this concept. The reaction of 2-cyclohexenone (7.3) with Grignard reagents in the presence of the chiral aminotroponeimine copper complex 7.5 as the catalyst in the presence of HMPA afforded the 1,4-adducts with 74% e.e. (Scheme 7.2). Since then several chiral catalysts based on Cu, Ni, or Co and a variety of chiral ligands have shown encouraging enantioselectivities in 1,4-additions of Grignard, organolithium, or dialkylzinc (R2Zn) reagents. Especially copper (I) catalysts, with ligands bearing "soft" phosphorus centers (7.5 or 7.6) showed promising results (Scheme 7.2).

Although good enantioselectivities can be obtained for both cyclic and acyclic enones, these catalytic reactions still show narrow substrate specificity. In general a catalyst that could be successfully employed for acyclic enones was not suitable for cyclic enones. Likewise a catalyst that gave good selectivity for cyclic enones yielded low selectivity for acyclic enones. This is most likely caused by the fact that the products are formed via

\[ \text{Scheme 7.2 Catalytic enantioselective conjugate additions.} \]

\[ \text{7.3 \xrightarrow{\text{RMgX or R}_2\text{Zn}} \text{7.4}} \]

\[ \text{7.5 (74 \% \text{ e.e.)}} \quad \text{7.6 (67-90\% \text{ e.e.)}} \quad \text{7.7 (32\% \text{ e.e.)}} \]

different organocopper intermediates following unique reaction pathways. Very recently Hayashi and co-workers reported the asymmetric 1,4-addition of aryl- and alkenyl-boronic acids which proceed with high enantioselectivity in the presence of a chiral phosphine-rhodium catalyst.\textsuperscript{15}

Recently considerable progress with regard to this undesired substrate specificity has been achieved by De Vries.\textsuperscript{16} Using BINOL derived phosphorus amidites 7.6 as a novel class of chiral monodentate ligand, for the first time both cyclic enones 7.3 and acyclic enones such as chalcone 7.7 could be employed to yield the desired 1,4-adducts with good enantioselectivities (Scheme 7.3).

![Scheme 7.3 Enantioselective conjugate addition of Et$_2$Zn to cyclic and acyclic enones.\textsuperscript{16}](image)

Employing either CuOTf or Cu(OTf)$_2$ the conjugate addition of diethylzinc (Et$_2$Zn) with cyclohexenone afforded the desired 1,4-adduct with 60% or 63% e.e., respectively. The reaction of Et$_2$Zn with chalcone yielded the 1,4-adduct with 90% e.e.. It should be noted that in case of Cu(OTf)$_2$, the actual chiral catalyst is probably a copper (I) complex which is formed by \textit{in situ} reduction of the copper (II) species. In all cases excellent regioselectivities (1,4- vs. 1,2-addition) were obtained.\textsuperscript{2}

Although the discovery of these novel chiral phosphorus amidites was an important breakthrough in the field of ligand accelerated conjugate additions, the realization of complete stereocontrol was only achieved after modular variation of the amine moiety of the ligand. The incorporation of two additional stereocenters into the amine part of the ligand, by employing (R,R)-bis(1-phenylethyl)amine and (S)-2,2’-BINOL for the synthesis of the ligand 7.9, resulted in a \textit{matched} combination and a highly selective catalyst for the Cu(OTf)$_2$ catalyzed addition of Et$_2$Zn to cyclohexenone which provided 7.4 in 94% yield and >98% e.e. (Scheme 7.4).\textsuperscript{17} The \textit{mismatched} (S,S,S) combination afforded the desired 1,4-adduct in 85%

yield but still 75% e.e. was found. Excellent yields and enantioselectivities ranging from 94% to > 98% were obtained for cyclohexenone and substituted cyclohexenones with a variety of unfuntionalized dialkylzinc compounds and zinc reagents bearing an ester or an acetal functionality when 7.9 was employed as the chiral ligand.

Scheme 7.4 Enantioselective conjugate addition of Et₂Zn to 7.3.

Subsequently the intermediate zinc-enolate initially formed after the conjugate addition, could be trapped by various aldehydes. In this way a highly regio- and enantioselective catalytic three-component coupling was achieved.¹⁸ For example, when enolate 7.10, formed in the reaction of 7.3 and Et₂Zn in the presence of Cu(OTf)₂ and ligand 7.9, was treated with benzaldehyde at -30 °C a 3:7 mixture of trans,erythro 7.11 and trans,threo 7.12 was obtained. Subsequent oxidation yielded a single isomer of 7.13 (Scheme 7.5).

Scheme 7.5 Enantioselective conjugate addition-tandem aldol reaction of cyclohexenone, Et₂Zn and benzaldehyde.

Using the Cu(OTf)$_2$ catalyzed conjugate addition of Et$_2$Zn in the presence of phosphorus amidite 7.9 a wide range of substrates can be employed with high enantioselectivities. Two major limitations have to be taken into account:

- Only six-membered and larger rings give high enantioselectivities (the analogous reactions of Et$_2$Zn to 2-cyclopentenone (7.17) gave the 1,4-adduct with 10% e.e.).$^{19}$
- $\alpha,\beta$-unsaturated esters are not reactive under the conditions that were employed.

In this chapter further investigations in the search of efficient ligand accelerated Cu(OTf)$_2$ catalyzed conjugate additions towards 2-cyclopentenone and to $\alpha,\beta$-unsaturated esters will be described.

$$\text{EtO} \quad \text{O} \quad \text{O} \quad \text{Et} \quad \text{Ph} \quad + \quad \text{Et}_2\text{Zn} \quad \xrightarrow{\text{2 mol % Cu(OTf)$_2$, 4 mol % L$^*$, toluene}} \quad \text{EtO} \quad \text{O} \quad \text{O} \quad \text{Et} \quad \text{Ph}$$

**Scheme 7.6** Cu(OTf)$_2$ catalyzed conjugate addition of Et$_2$Zn to benzalmalonate 7.14a.

### 7.3 Cu(OTf)$_2$ catalyzed conjugate addition of Et$_2$Zn to $\alpha,\beta$-unsaturated esters

Compared to enones the reactivity of $\alpha,\beta$-unsaturated esters with respect to conjugate additions is much lower.$^2$ When $\alpha,\beta$-unsaturated esters were used as the Michael acceptor in the Cu(OTf)$_2$ catalyzed conjugate addition of Et$_2$Zn, no addition reaction occurred, even after prolonged reaction times or at elevated reaction temperature.$^{20}$ Benzalmalonate 7.14a, however, afforded the 1,4-adduct 7.15a in a very clean reaction with a moderate e.e. (35%), as was shown by De Vries.$^{16}$ The activation of 7.14a by two ester groups makes the double bond more reactive for nucleophilic attack, and since 7.15a can in principle be converted into $\beta$-substituted cinnamic acid ester 7.16 it can act as a synthetic analog of $\alpha,\beta$-unsaturated esters. These encouraging preliminary experiments and the lack of further examples of catalytic enantioselective conjugate additions of organometallic reagents to $\alpha,\beta$-unsaturated esters in the literature prompted us to study this reaction further in order to improve the enantioselectivity.

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$^{19}$ For 2-cycloheptenone the e.e. was incorrectly reported to be 53%.$^{17}$ Control experiments however showed that for 2-cycloheptenone the e.e. was 98.8% under the reported conditions. See Naasz, R., forthcoming thesis, University of Groningen.

$^{20}$ Ref. 16: p 119.
The introduction of methyl substituents at the 3,3'-positions of the BINOL moiety as present in phosphorus amidite \(7.17\) resulted in a slight decrease in enantioselectivity (29\% e.e.) in the conjugate addition. The use of the more rigid ligand \(7.18\) also yielded \(7.15a\) with a slightly lower e.e. (33\%). Using phosphorus amidite \(7.19\) that contains two methyl groups at the amine moiety resulted in a drop in enantioselectivity to 17\%. The best results were obtained when \(7.9\) was used as the ligand for the conjugate addition of \(\text{Et}_2\text{Zn}\) with \(7.14a\) and \(7.15a\) was obtained in quantitative yield with 40\% e.e.

Since the use of alternative ligands did not result in a significant enhancement of the enantioselectivity, it was attempted to improve the selectivity by applying different ester functionalities. When dibenzyl benzalmalonate \(7.14b\) was employed as the Michael acceptor, with either \(7.6\) or \(7.9\), \(7.15b\) was obtained with 35\% and 40\% e.e., respectively. The stereochemical outcome of the conjugate addition was not influenced on going from an ethyl to a benzyl ester. The e.e. was, however, influenced significantly when isopropylidene benzalmalonate \(7.14c\), derived from Meldrum's acid, was used, in order to reduce the conformational freedom of the substrate. The 1,4-adduct \(7.15c\) was isolated in racemic form with \(7.9\) as the ligand. Apparently the orientation of the carbonyl (presumably coordinated to Zn\(^{16}\)) is essential for stereocontrol.

![Image of modified phosphorus amidites](image.png)

**Figure 7.1** Modified phosphorus amidites for conjugate addition to \(7.14a\).

![Scheme 7.7 Variation of substrate](scheme.png)

**Scheme 7.7** Variation of substrate.

In summary, the enantioselectivity of the Cu(OTf)\(_2\) catalyzed conjugate addition of \(\text{Et}_2\text{Zn}\) to benzalmalonates could be improved to 40\% by using \(7.9\) as the ligand. Attempts to improve the enantioselectivity of the reaction by altering the ester were, however, not successful.
7.4 Catalytic enantioselective conjugate addition-tandem aldol reaction with 2-cyclopentenone

Enantioselectivities of > 98% could be achieved with cyclohexenones and larger cycloalkenones using 7.9 as a ligand in the Cu(OTf)$_2$ catalyzed conjugate addition of organozinc reagents.$^{19}$ In sharp contrast the addition of Et$_2$Zn to cyclopentenone furnished the Michael adduct with only 10% e.e. using this ligand. Furthermore the yield was very low probably due to coupling and oligomerisation of the enone and the intermediate zinc enolate. Several phosphorus amidites derived from BINOL and from TADDOL were examined as ligands in the copper catalyzed conjugate addition of diethyl zinc to cyclopentenone in attempts to improve the yield and selectivity.

![Scheme 7.8 Conjugate addition of Et$_2$Zn to 2-cyclopentenone.](image)

This undesired side reaction could partially be circumvented by working at lower temperatures (-80 °C); however, the reaction was sluggish at this temperature and the yield of the reaction never exceeded 58%. Furthermore the results were difficult to reproduce, because of the extreme volatility of the product and because the formation of side products could not be completely suppressed. High yields could, however, be obtained when benzaldehyde was added to the reaction mixture for the in situ quenching of the zinc enolate. Using this protocol, 2,3-disubstituted cyclopentanones were obtained in 80-85% isolated yield as a mixture of trans-erythro and trans-threo isomers 7.21 via a conjugate addition-tandem aldol reaction.$^{17,18}$ Oxidation of the mixture of isomers of 7.21 with pyridinium chlorochromate furnished 7.22 in 60-70% isolated yield as a single isomer. It should be noted that no trace of 1,2-addition of Et$_2$Zn to benzaldehyde was found in this three component coupling reaction.

![Scheme 7.9 Enantioselective conjugate addition-tandem aldol reaction.](image)

7.4.1 Variation of the BINOL derived phosphorus amidite ligands

The reaction described above is much slower then the simple conjugate addition of Et$_2$Zn with cyclohexenone with the same catalyst, which is complete within three hours. The three component coupling reaction requires reaction times of a day to achieve complete
conversion of the starting material. The three component coupling reaction, however, proved to be an easy reaction to test a range of BINOL derived phosphorus amidites. The results are listed in Table 1.

**Table 1** Effect on the enantioselectivity of the conjugate addition-tandem aldol reaction of cyclopentenone of modular variation of BINOL phosphorus amidites.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>Trans-erythro : trans-threo(^a)</th>
<th>e.e.(^b,c)</th>
</tr>
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<tbody>
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<td>39:61</td>
<td>2</td>
</tr>
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<td>7.18</td>
<td>40:60</td>
<td>5</td>
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<tr>
<td>4</td>
<td>7.23</td>
<td>45:55</td>
<td>6</td>
</tr>
<tr>
<td>5</td>
<td>7.24</td>
<td>42:58</td>
<td>7</td>
</tr>
<tr>
<td>6</td>
<td>7.25</td>
<td>47:53</td>
<td>9</td>
</tr>
<tr>
<td>7</td>
<td>7.9</td>
<td>40:60</td>
<td>10 (4)</td>
</tr>
<tr>
<td>8</td>
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<td>37:63</td>
<td>30</td>
</tr>
<tr>
<td>9</td>
<td>7.27</td>
<td>43:57</td>
<td>37</td>
</tr>
<tr>
<td>10</td>
<td>7.17</td>
<td>42:58</td>
<td>3</td>
</tr>
</tbody>
</table>

\(^a\) Determined by \(^1\)H-NMR signals of the benzylic protons of the crude product mixture at 5.1 and 4.6 ppm respectively. \(^b\) e.e. determined after conversion into 7.22, absolute configuration: S,S. \(^c\) Numbers in parentheses for reaction in hexane.

The major part of the BINOL derived phosphorus amidites induce a low enantioselectivity in the three component coupling reaction. Introduction of sterically demanding groups did not influence the e.e. beneficially and the use of a phosphorus amidite
with methyl groups at the 3- and 3'-position of the BINOL moiety also only led to a marginal influence on the stereochemical outcome of the reaction. However, when phosphorus amidite 7.27 was used with an additional coordinating moiety, the three component coupling reaction furnished 7.18 with an e.e. of 37%. Furthermore, when the reaction was performed under the influence of 7.26, (the mismatched ligand in the reaction of cyclohexenone with Et₂Zn (vide supra)), adduct 7.18 was isolated with an e.e. of 30%. Surprisingly the reaction under the influence of 7.9, the matched ligand in the reaction of cyclohexenone with Et₂Zn (vide supra), yielded 7.18 with 10% e.e.. Hence the matched ligand for cyclohexenone and larger cyclic enones appears to be the mismatched ligand for cyclopentenone. This result together with the lower reactivity (vide supra) suggests that ethyl transfer to cyclopentenone proceeds via a different reaction pathway or reaction intermediates then for the larger rings.

![Figure 7.2 Structures of phosphorus amidites 7.30-7.36](image)

Most BINOL derived phosphorus amidites that were prepared up till now were very stable towards both moisture and oxidation and storage under an inert atmosphere was not necessary. Those bearing an additional coordinating moiety in the amine part of the ligand were less stable. Although the initial formation of amidites 7.31-7.34 could be observed by phosphorus NMR, only 7.27 could be isolated in a pure form and had to be stored under argon atmosphere, whereas in the other cases only oxidized products could be isolated. Furthermore, it was not possible to isolate ligands 7.28-7.30. Probably due to steric reasons these phosphorus amidites are sensitive towards hydrolysis and decompose during the isolation.

### 7.4.2 Influence of solvent and additives

All conjugate addition reactions described up till now have been performed in toluene and the use of hexane did not result in an increase in enantioselectivity (Table 1, entry 2 and
8, numbers in parenthesis). In fact the e.e.'s were reduced to 4% and 5% when 7.9 or 7.6 were employed as the ligands, respectively. Further lowering of the reaction temperature did not influence the e.e. of the product either.

Next the influence of additives to the three component coupling reaction was investigated (Scheme 7.9). The addition of imidazole (0.01 (5% e.e.) or 0.02 (2% e.e) equiv.) or MeOH (0.01 (2% e.e.) or 0.02 (0% e.e.) equiv.) as external extra coordinating moieties resulted in a lowering of the enantioselectivity of the reaction, when the conjugate addition-tandem aldol reaction was performed under the influence of 7.6 and Cu(OTf)$_2$. Surprisingly the addition of a small amount of water to the reaction mixture, which caused a partial hydrolysis of the organozinc reagent, resulted in the formation of 7.21 though in only 38% yield, with an e.e. of 27%. The major enantiomer of the product had the opposite configuration compared to the major enantiomer that was formed without the addition of water.

The zinc salts that are formed due to the hydrolysis of the zinc reagent$^{21}$ might function as additional ligands in the ethyl transferring step, which apparently results in a more selective reaction. However, the effect of the addition of water has to be studied in more detail.

### 7.5 TADDOL derived phosphorus amidites

#### 7.5.1 Synthesis and characteristics

An alternative class of C$_2$-symmetric diols that is frequently used for catalytic enantioselective transformations are TADDOLs 7.35.$^{22,23}$ These ligands are readily available in both enantiomeric forms from tartaric acid. Although it was suggested by de Vries$^{16}$ that the stability of phosphorus amidites derived from TADDOL was lower than that of the BINOL analogs, the reaction of (R,R)-TADDOL with hexamethylphosphorous triamide (HMPT) in chloroform afforded the corresponding phosphorus amidite 7.36 in high yield (Scheme 7.10).$^{24}$

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$^{23}$ A sample of 7.36 was kindly provided by Thomas Schrader from the University of Düsseldorf.
Phosphorus amidite 7.36 was stable towards air and moisture and storage under an inert atmosphere was not necessary similar to the BINOL derived phosphorus amidites. For the synthesis of modified TADDOL derived phosphorus amidites an alternative route had to be employed because the analogous phosphorus triamides were not available. Phosphorus amidites 7.38-7.40 were, however, readily available using a procedure that was also used for the BINOL analogs.\textsuperscript{16} The reaction of (R,R)-TADDOL with PCl\textsubscript{3} afforded phosphorus chloride 7.37 which after nucleophilic substitution with a number of appropriate \textit{in situ} prepared secondary lithium amides furnished the corresponding phosphorus amidites (Scheme 7.11).

Using diisopropylamine, dibenzylamine and piperidine 7.38-7.40 were synthesized in 30\%, 34\% and 55\% yield, respectively. Although the yield of the crude products were satisfactory, the isolated yields of the pure compounds were sometimes low due to problems with the purification. No attempts have been made so far to optimize the isolated yield. The reaction of modified TADDOLs, which had either a cyclopentanyl acetal group or \textit{ortho}-methylphenyl groups, furnished with HMPT the analogous phosphorus amidites 7.41 and 7.42 in 45\% and 25\% yield, respectively.
Satisfactory $^1\text{H}$, $^{13}\text{C}$ and $^{31}\text{P}$-NMR spectra could be obtained for all compounds except for 7.42 which showed broad signals in the $^1\text{H}$ NMR spectrum at room temperature, probably due to hindered rotation of the aryl groups. When the $^1\text{H}$-NMR spectrum was recorded at 80 °C in CDCl$_3$, sharp signals could be realized, but, due to decomposition of 7.42 at these temperatures no $^{13}\text{C}$-NMR could be obtained. The $^1\text{H}$-NMR spectra of the TADDOL derived phosphorus amidites showed some interesting characteristics (Figure 7.4). First of all two signals are present for the two bridgehead protons, a doublet for the proton that points in the opposite direction to the phosphorus lone pair and a double doublet as a result of a phosphorus coupling for the proton that is pointing in the same direction. This shows that due to the introduction of the phosphorus the ligand is no longer $C_2$-symmetric. Furthermore one of the acetal methyl groups is shifted to high field due to an aromatic anisotropy effect, which indicates that this group is located near one of the phenyl rings, whereas the absorption for other methyl is found in the expected region.
In order to explain the peculiar $^1$H NMR shifts of the TADDOL derived phosphorus amidites, the structural features were investigated using X-ray crystallography. Crystallization of 7.36 from chloroform afforded crystals suitable for X-ray analysis. The molecular structure is shown in figure 7.4 and selected bond distances and bond angles are listed in Table 3 and 4. The free ligand has a triclinic geometry with a PN distance of 1.647(3) which is in good agreement with the bond length found in the molecular structure of 7.19, and other trivalent phosphorus amidites reported in the literature. The geometry of the amine group of 7.36 is planar and a similar structural feature is found in 7.19. However, whereas in 7.19 the alkyl groups on the nitrogen are oriented perpendicularly to the lone pair of the phosphorus, the alkyl groups in 7.36 point in the same direction as the lone pair of the phosphorus, i.e. a 90 ° rotation around the PN bond has occurred. Furthermore, it can be seen that the molecular structure is not $C_2$-symmetric and that one of the methyl groups of the acetal segment is indeed located near one of the phenyl groups. A similar preliminary

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26 Dr. R. Hulst, unpublished results.
molecular structure was found for 7.38 but the quality of the crystals was too poor to obtain a satisfactory R value.28

7.5.2 Examination of TADDOL based phosphorus amidites as chiral ligands in the conjugate addition of Et₂Zn to cyclic enones.

Before testing the ligands described in the previous section, in the three component coupling reaction with cyclopentenone, the effect of several of these ligands was examined in the copper catalyzed ethyl transfer reaction from Et₂Zn to cyclohexenone. Under the influence of 2.4 mol% of ligand and 1.2 mol% of Cu(OTf)₂ the reaction of Et₂Zn and cyclohexenone was performed in toluene at -35 °C. Complete conversion of the starting enone was accomplished within 3 h, furnishing 7.4 in > 80% isolated yield.

\[
\begin{align*}
\text{O} & \quad + \quad \text{Et}_2\text{Zn} \\
& \quad \xrightarrow{1.2 \text{ mol}\% \text{ Cu(OTf)}_2} \\
& \quad \xrightarrow{2.4 \text{ mol}\% \text{ L}^*} \\
& \quad \text{toluene, -35 °C} \\
\end{align*}
\]

**Scheme 7.12 Copper catalyzed conjugate addition of Et₂Zn to cyclohexenone.**

Under the influence of ligand 7.36, the 1,4-adduct (R)-7.4 was obtained with an e.e. of 57% in 84-87% isolated yield. Lowering of the reaction temperature or changing the amount of catalyst did not influence the enantioselectivity of the reaction. However, when 1.2 mol% Cu(OTf)₂ and 1.2 mol% or 3.6 mol% of 7.36 were used the e.e.'s dropped to 47% and 48%, respectively. Slow addition of the Et₂Zn or of cyclohexenone over a period of 1.5 h resulted in a decrease in enantioselectivity to 35% and 51%, respectively. Upon addition of powdered molecular sieves (4 Å) to the reaction mixture, the enantioselectivity of the conjugate addition increased to 71%. This unexpected rise in e.e. might be caused by the presence of trace amounts of water which could result in the formation of mixed zinc hydroxide intermediates21 that can play a role as additional ligand (**vide supra**). Alternatively the reaction could take place at the surface of the sieves.29 The use of molecular sieves, dried at 250 ° under reduced pressure (ca. 15 mmHg), resulted in a slight decrease in enantioselectivity; e.e. = 66% when 3 Å or 4 Å sieves were used and e.e. = 60% with 5 Å sieves.

It has recently been reported that molecular sieves improve the stereoselectivity in some titanium catalyzed reactions such as the Sharpless epoxidation,30 Diels-Alder reactions,31 and glyoxylate ene reactions.32 Similar effects were observed in the aluminium

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catalyzed ene reaction of prochiral aldehydes, and palladium catalyzed oxidative cyclizations.

Molecular sieves, a type of zeolite, are crystalline microporous aluminosilicates with a three dimensional framework containing cavities of molecular dimensions (3-10 Å). The polymeric framework consist of AlO$_4$ and SiO$_4$ tetrahedra linked by shared oxygen atoms. The pores normally contain water of hydration which can be removed by heating without causing the three-dimensional network to collapse. Dehydrated zeolites are able to absorb both water and organic compounds. The effect of molecular sieves in, for example, the epoxidation of allylic alcohols has been attributed to its water trapping properties, since water has been shown to lower the enantioselectivity and the reaction rate by interacting with the catalyst. However, the results presented here clearly indicate that the role of the molecular sieves in the conjugate addition of diethylzinc to cyclic enones is not to eliminate water from the reaction system. In contrast, the presence of water is beneficial to the stereoselectivity. The composition and structure of the zeolites are clearly of importance, since different size molecular sieves show a variance in enantioselectivity. The enhanced e.e.’s in Et$_2$Zn reactions is highly remarkable in view of the sensitivity of R$_2$Zn reagents to hydrolysis.

Under the influence of ligand 7.38 without the use of molecular sieves to our surprise racemic 1,4-adduct 7.4 was obtained (Scheme 7.12). Contrary to the results with BINOL derived phosphorus amidites, the introduction of sterically demanding substituents on the amine part of the ligand causes a decrease in enantioselectivity. This might be due to the different orientation of the alkyl substituent at the amine part of the ligands (vide supra). In the presence of 2.4 mol% of 7.41, powdered molecular sieves and Cu(OTf)$_2$ (1.2 mol%) 7.4 with 58% e.e. was obtained.

Next the effect of the TADDOL derived ligands on the three component coupling reaction with cyclopentenone was examined (Scheme 7.13). Using 7.28 2,3-disubstituted cyclopentanone 7.21 was obtained in 85% isolated yield as a mixture of trans-erythro and trans-threo isomers via the conjugate addition-tandem aldol reaction. PCC oxidation of 7.21 afforded diketone 7.22 with an e.e. of 37%. The addition of molecular sieves also increased the enantioselectivity in the conjugate addition-tandem aldol reaction yielding 7.21 with an e.e. of 62%.

Next, we have tested several TADDOL derived phosphorus amidites that were prepared by a variation of the TADDOL and the amine moieties in these ligands. The results are outlined for the tandem conjugate addition reaction to cyclopentenone in Table 3.

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Scheme 7.13

Table 3 Effect of modular modifications of the TADDOL phosphorus amidite ligands on the tandem conjugate-aldol reaction of 7.20.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ligand</th>
<th>trans-erythro : trans-threo&lt;sup&gt;a&lt;/sup&gt;</th>
<th>e.e.</th>
<th>Absolute configuration</th>
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<td>62</td>
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<td>4&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>24&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>6</td>
<td>7.42</td>
<td>45:55</td>
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</table>

<sup>a</sup> Determined by <sup>1</sup>H-NMR signals of the benzylic protons of the crude product mixture at 5.1 and 4.6 ppm respectively. <sup>b</sup> No molecular sieves were added.

Omission of sieves (entry 2 and 4) and introduction of additional steric bulk on the amine part of the ligand resulted in a drastic drop in enantioselectivity (entries 3 and 4). Modification of the acetal part of the phosphorus amidite (7.41) also affected the enantioselectivity (entry 5). To our surprise racemic product was isolated when a phosphorus amidite derived from α,α,α',α'-tetra-(o-methylphenyl)-2,2'-dimethyl-1,3-dioxolane-4,5-dimethanol (7.42) was used (entry 6). When the BINOL derived phosphorus amidites and the TADDOL derived analogs are compared, it is remarkable that whereas in the first case enhanced steric hindrance at the amine part increases the enantioselectivity to a large extent, in the latter case the opposite effect is observed. The negative influence of the sterically more demanding amine part of the ligands can be explained by the fact that one of the alkyl groups at the planar amine points in the same direction as the lone pair of the phosphorus. This is clearly seen in the molecular structure of 7.36. Furthermore hindered rotation of the aromatic groups in ligand 7.42 prevents the preferential formation of a single well defined complex in solution, which might result in a nonselective reaction (entry 6).

Omission of benzaldehyde in the reaction of Et₂Zn with 2-cyclopentenone resulted, at low temperature (-78°C), in the formation of 3-ethylcyclopentanone 7.43 (Scheme 7.14). 128
Although it was reported in the literature that the e.e. of 7.43 could be determined by chiral HPLC\textsuperscript{36} we could not determine an exact value of the e.e.. Based on partly separated peaks, the e.e. of 7.43 was estimated to be 60%, which indicates that benzaldehyde does not influence the enantioselectivity of the ethyl transfer to 2-cyclopentenone.

\[
\begin{align*}
\text{O} & \quad + \quad \text{Et}_2\text{Zn} \\
toluene, -78 \, ^\circ \text{C} & \quad \xrightarrow{1.2 \, \text{mol\% Cu(OTf)}_2} \\
& \quad \xrightarrow{2.4 \, \text{mol\% 7.36}} \\
& \quad \xrightarrow{\text{mol sieves}} \\
7.43 & \sim 60 \% \text{ e.e}
\end{align*}
\]

\textbf{Scheme 7.14}

7.6 \textit{Conclusions and prospects}

Considerable progress has been made with respect to the enantioselectivity of the ligand accelerated conjugate addition of Et\textsubscript{2}Zn to 2-cyclopentenone. Using the three component coupling reaction of 2-cyclopentenone, Et\textsubscript{2}Zn and benzaldehyde a rapid method has been found efficiently to examine novel ligands for this reaction. The most striking observation in the BINOL phosphorus amidite catalyzed reactions is the fact that the mismatched ligand 7.26 for the conjugate addition to 2-cyclohexenone appeared to be the matched ligand for the conjugate addition to 2-cyclopentenone. This is a clear indication that different reaction intermediates are involved in the two reactions. The highest enantioselectivity was obtained using ligand 7.27 with an additional coordinating moiety. This type of ligand is, however, much more sensitive towards moisture and air which is reflected in the unsuccessful attempts so far to synthesize alternative ligands bearing an additional coordinating moiety.

Several novel TADDOL derived phosphorus amidites have been prepared and characterized. Compared to the BINOL phosphorus amidites higher enantioselectivities were obtained in the three component coupling reaction. Contrary to the results obtained with BINOL phosphorus amidites in the conjugate addition of dialkylzinc to cyclohexenone, the introduction of steric demand in the amine part of the ligand resulted in less selective reactions with 2-cyclopentenone. Unexpected enhancement of enantioselectivity was observed upon the addition of powdered molecular sieves. Although the enhanced e.e.'s in Et\textsubscript{2}Zn reactions are highly remarkable in view of the sensitivity of R\textsubscript{2}Zn reagents to hydrolysis, the presence of trace amounts of water is probably the cause of the observed raise in enantioselectivity.

7.7 Experimental section

General

All reactions described in this chapter were performed under N\textsubscript{2} in flame-dried standard Schlenk equipment. Toluene and THF were distilled from sodium immediately prior to use. \textsuperscript{31}P NMR spectra were recorded on a Varian Gemini 100 at 80.95 MHz. For all other general remarks, see the experimental section of chapter 3.

Materials

The following compounds were commercially available and used without purification: diethyl benzalmalonate (7.14a, Acros), Cu(O\textsubscript{2}F\textsubscript{2}) (Aldrich), 2-cyclopenten-1-one (Aldrich), PCl\textsubscript{3} (Merck), diethylzinc (1.0 M in hexanes; 1.1 M in toluene; Aldrich), dibenzylmalonate (Fluka), piperidine (Aldrich), Meldrum's acid (Aldrich, or prepared according to a literature procedure\textsuperscript{37}), pyridinium chlorochromate (Aldrich), Tris(dimethylamino)phosphine (HMPT) (Fluka), molecular sieves (3-5 Å, Merck). Chiral BINOL derived phosphorus amidites 7.6, 7.17-7.19 and 7.23-7.25 were kindly provided by Dr. A.H.M. de Vries, 7.9 and 7.26 by mr. A. Arnold and 7.27 by mr. R. La Crois. All TADDOL derivatives were prepared according to a literature procedure by mr. J. Maurer and Dr. A. van Oeveren.\textsuperscript{38,23}

Dibenzyl benzalmalonate (7.14b)

A mixture of dibenzyl malonate (6.0 g, 0.021 mol), benzaldehyde (2.38 g, 0.022 mol) and piperdine (0.2 mL) in toluene (50 mL) was refluxed overnight. After cooling to room temperature the solvent was evaporated and the residual oil was purified by column chromatography (SiO\textsubscript{2}, hexanes:ethyl acetate= 9:1) to yield 5.6 g (0.015 mol, 72%) of 7.14b as a nearly colorless solid. \textsuperscript{1}H-NMR (300 MHz, CDCl\textsubscript{3}) δ = 5.18 (s, 4H), 7.24 (m, 15H), 7.69 (s, 1H); \textsuperscript{13}C-NMR (75 MHz, CDCl\textsubscript{3}) δ = 67.16 (t), 67.55 (t), 77.42 (s), 125.58 (s), 127.99 (d), 128.25 (d), 128.42 (d), 128.51 (d), 128.54 (d), 128.75 (d), 128.79 (d), 129.47 (d), 130.60 (d), 132.59 (s), 134.78 (s), 135.45 (s), 143.17 (d), 163.82 (d), 166.30 (s); HRMS calcd. for C\textsubscript{24}H\textsubscript{20}O\textsubscript{4}: 372.136, found 372.137.

Isopropylidene benzalmalonate (7.14c)

Prepared according to a literature procedure in 60% yield.\textsuperscript{39} mp 71 °C; \textsuperscript{1}H-NMR (300 MHz, CDCl\textsubscript{3}) δ = 1.70 (s, 6H), 7.37 (m, 3H), 7.94 (d, J \textsubscript{3} = 7.3 Hz, 2H), 8.32 (s, 1H); \textsuperscript{13}C-NMR (75 MHz, CDCl\textsubscript{3}) δ = 27.54 (q), 104.51 (s), 114.75 (s), 128.65 (d), 131.62 (s), 133.53 (d), 133.60 (d), 158.03 (d), 163.19 (s).


General procedure for conjugate additions to benzalmalonates (7.14)

A solution of flame dried Cu(OTf)$_2$ (4.5 mg, 0.012 mmol) and chiral amidite (0.024 mmol) in toluene (5.0 mL) was stirred at ambient temperature for 1-2 h under N$_2$ atmosphere. Normally this results in a slightly turbid solution. The solution was cooled to -35 to -40 °C and substrate (1.0 mmol) was added. Then Et$_2$Zn in toluene (1.1 M, 1.5 equiv.) was slowly added (ca. 30 sec) and stirring was continued at -35 °C overnight. Saturated NH$_4$Cl solution (10 mL, aq.) was added and after separation of the layers the aqueous layer was extracted with ether (2 x 20 mL). The combined organic layers were dried (Na$_2$SO$_4$) and evaporated to dryness to yield the 1,4-adduct 7.15. The purification procedure for the 1,4-adducts is described below. A sample (ca. 0.2 mmol) of the 1,4-adducts (7.15a-c) was reduced using LiAlH$_4$ solution in THF to afford the corresponding diol 7.16 in ca. 85% yield, after work up with saturated NH$_4$Cl solution. The e.e. of 7.16 was determined by HPLC analysis using a chiral stationary phase (DAICEL CHIRALPAK OJ, iPrOH:hexane 1:19, 1.0 mL/min, RT, $T_r$ = 26.9, $T_r$ = 37.4.

1-Hydroxy-2-hydroxymethyl-3-phenylpentane (7.16) $^1$H-NMR (200 MHz, CDCl$_3$) $\delta$ = 0.70 (t, $J$ = 7.3 Hz, 3H), 1.48-1.69 (m, 1H), 1.76-1.97 (m, 2H), 2.50-2.62 (m, 1H), 2.0-3.5 (br, 2H), 3.36-3.45 (m, 1H), 3.56-3.36 (m, 1H), 3.76-3.86 (m, 1H), 396 (dd, $J$ = 10.9 Hz, $J$ = 3.4 Hz, 1H), 7.10-7.34 (m, 5H); $^{13}$C-NMR (50 MHz, CDCl$_3$) $\delta$ = 12.16 (q), 25.90 (t), 45.51 (d), 46.61 (d), 64.32 (t), 64.66 (t), 126.26 (d), 128.24 (d), 128.34 (d), 143.04 (s).

Diethyl 1-phenylpropylmalonate (7.15a)

Prepared according to the general procedure in 98% yield, after purification by flash chromatography (SiO$_2$, hexanes:ethyl acetate=9:1). $^1$H-NMR (200 MHz, CDCl$_3$) $\delta$ = 0.74 (t, $J$ = 7.3 Hz, 3H), 0.95 (t, $J$ = 7.1 Hz, 3H), 1.31 (t, $J$ = 7.1 Hz, 3H), 1.58-1.78 (m, 2H), 3.27 (dt, $J$ = 10.9 Hz, $J$ = 3.7 Hz, 1H), 3.64 (d, $J$ = 10.9 Hz, 1H), 3.88 (q, $J$ = 7.1 Hz, 2H), 4.24 (q, $J$ = 7.1 Hz, 2H), 7.15-7.33 (m, 5H); $^{13}$C-NMR (50 MHz, CDCl$_3$) $\delta$ = 11.70 (q), 13.68 (q), 14.10 (q), 27.04 (t), 47.32 (d), 58.68 (d), 61.05 (t), 61.47 (t), 125.26 (d), 126.80 (d), 128.21 (d), 128.39 (d), 129.00 (d), 140.88 (s), 168.64 (s).$^{16}$

Dibenzyl 1-phenylpropylmalonate (7.15b)

Prepared according to the general procedure in 91% yield as a colorless oil, after purification by flash chromatography (SiO$_2$, hexanes:ethyl acetate=9:1). $^1$H-NMR (200 MHz, CDCl$_3$) $\delta$ = 0.59 (t, $J$ = 7.3 Hz, 3H), 1.45-1.67 (m, 2H), 3.19 (dt, $J$ = 3.7 Hz, $J$ = 11.0 Hz, 1H), 3.68 (d, $J$ = 11.0 Hz, 1H), 4.73 (m (diastereotopic), $J$ = 12.5, 2H), 5.09 (s, 2H), 6.89-6.92 (m, 2H), 7.05-7.24 (m, 13H); $^{13}$C-NMR (50 MHz, CDCl$_3$) $\delta$ = 12.26 (q), 27.51 (t), 47.94 (d), 59.24 (d), 67.46 (t), 67.78 (t), 127.50 (d), 128.62 (d), 128.68 (d), 128.95 (d), 129.15 (d), 135.76 (s), 135.76 (s), 141.05 (s), 168.21 (s), 168.82 (s); HRMS calcd. for C$_{26}$H$_{26}$O$_4$: 402.183, found: 402.183.
Isopropylidene 1-phenylpropylmalonate (7.15c)\textsuperscript{40}

Prepared according to the general procedure in 93% yield as a white solid, after purification by flash chromatography (SiO\textsubscript{2}, hexanes:ethyl acetate=4:1). \textsuperscript{1}H-NMR (200 MHz, CDCl\textsubscript{3}) \(\delta = 0.85\) (t, \(J = 7.3\) Hz, 3H), 1.01 (s, 3H), 1.52 (s, 3H), 1.92-2.07 (m, 1H), 2.13-2.25 (m, 1H), 3.52-3.61 (m, 2H), 7.05-7.21 (m, 5H); \textsuperscript{13}C-NMR (50 MHz, CDCl\textsubscript{3}) \(\delta = 12.31\) (q), 25.38 (t), 27.76 (q), 28.19 (q), 47.90 (d), 50.79 (d), 105.34 (s), 127.56 (d), 128.09 (d), 128.60 (d), 128.89 (d), 139.35 (s); HRMS calcd. for C\textsubscript{15}H\textsubscript{18}O\textsubscript{4}: 262.120, found: 262.120.

General procedure for the conjugate addition-tandem aldol reaction

A solution of flame dried Cu(OTf)\textsubscript{2} (4.5 mg, 0.012 mmol) and chiral amidite (0.024 mmol) in toluene (5.0 mL) was stirred at ambient temperature for 1-2 h under N\textsubscript{2} atmosphere. Normally this results in a slightly turbid solution. The solution was cooled to -35 to -40 °C and 2-cyclopentenone (82 \(\mu\)L, 0.98 mmol) and benzaldehyde (100 \(\mu\)L, 0.98 mmol) were added. Et\textsubscript{2}Zn was slowly added (ca. 30 sec) and stirring was continued at -35 °C for 24h. Saturated NH\textsubscript{4}Cl solution (10 mL, aq.) was added and after separation of the layers the aqueous layer was extracted with ether (2 x 20 mL). The combined organic layers were dried (Na\textsubscript{2}SO\textsubscript{4}) and evaporated to dryness to yield 7.17 as an oil that solidified upon standing to yield ca.0.225 g of white solid. Purification using flash chromatography (SiO\textsubscript{2}, hexanes:ethyl acetate=7:3) yielded pure 7.21 as a mixture of trans-three and trans-erythro isomers\textsuperscript{41} in 80-85% isolated yield as a white solid. \textsuperscript{1}H-NMR (300 MHz, CDCl\textsubscript{3}) \(\delta = 0.57\) (t, \(J =7.3\) Hz, ca.1.5H), 0.66 (t, \(J = 7.4\) Hz, ca.1.5H), 0.73-1.17 (m, ca.1.5H), 1.26-1.32 (m, ca.1.5H), 1.63-1.70 (m, ca.0.5H), 1.86-2.34 (m, ca.4.5H), 3.25-3.45 (br, ca.0.5H, (minor isomer)), 4.12-4.28 (br, ca.0.5H, (major isomer)), 4.64 (d, \(J = 7.7\) Hz, ca.0.5H, (major isomer)), 5.09 (d, \(J = 3.7\) Hz, ca.0.5H, (minor isomer)), 7.12-7.35 (m, 5H). \textsuperscript{13}C-NMR (75 MHz, CDCl\textsubscript{3}) \(\delta =11.55\) (q), 11.74 (q), 27.02 (t), 27.22 (t), 27.58 (t), 28.07 (t), 38.75 (t), 39.03 (d), 39.58 (t), 41.33 (d), 60.42 (d), 69.81 (d), 73.38 (d), 75.76 (d), 112.36 (d), 127.36 (d), 127.95 (d), 128.65 (d), 128.89 (d), 128.96 (d), 141.84 (s), 142.76 (s), 202.30 (s), 203.45 (s);\textsuperscript{18} A sample of 7.21 (35 mg, 0.16 mmol) was dissolved in dry dichloromethane (2 mL) molecular sieves were added (4 Å, ca. 100 mg) and the mixture was stirred at 0 °C. Pyridinium chlorochromate (PCC, 50 mg, 0.23 mmol) was added and stirring was continued for 2 h. Diethyl ether was added (5.0 mL) and after filtration over celite the solvent was evaporated. The residual brown oil was purified by flash chromatography (SiO\textsubscript{2}, hexanes:ethyl acetate=9:1) to afford 7.22 as a colorless oil in 60-70% isolated yield. \textsuperscript{1}H-NMR (200 MHz, CDCl\textsubscript{3}) \(\delta = 0.90\) (t, \(J = 6.9\) Hz, 3H), 1.42-1.62 (m, 4H), 2.37-2.52 (m, 2H), 2.83-2.91 (m, 1H), 3.94 (d, \(J = 9.0\) Hz, 1H), 7.52-8.00 (m, 5H); \textsuperscript{13}C-NMR (50 MHz, CDCl\textsubscript{3}) \(\delta = 11.79\) (q), 26.64 (t), 27.72 (t), 39.12 (t), 42.17 (d), 63.78 (d), 127.74 (d), 129.14 (s), 133.27 (d), 197.43 (s), 213.20 (s). The e.e. of 7.22 was determined by HPLC analysis on a chiral

\textsuperscript{40} Haslego, M.L., Smith, F.X. Synth. Commun. 1980, 10, 421.

\textsuperscript{41} The ratios are listed in Table 3.
stationary phase (DAICEL CHIRALPAK OJ, iPrOH:hexane 1:19, 1.0 mL/min, RT, \( T_r = 15.0 \) min \((R,R)\), \( T_r = 21.7 \) min \((S,S)\)).

\((1R,7R)-4-N,N-Dimethylamino-9,9-dimethyl-2,2,6,6-tetraphenyl-3,5,8,10-tetraoxo-4-phosphabicyclo[5,3,0]decane (7.36)\)

\(\alpha,\alpha,\alpha',\alpha'-\text{Tetraphenyl-2,2'-dimethyl-1,3-dioxolane-4,5-dimethanol (TADDOL)}\) (10.0 g, 21.4 mmol) was dissolved under argon in dry chloroform (50.0 mL) and HMPT (4.2 g, 4.7 mL, 25.7 mmol) was added dropwise with a syringe. The mixture was heated to reflux for 12-16 h. After 2 h the product begins to precipitate. At the end of the reaction the mixture is cooled to room temperature and the product is filtered off, washed with dry chloroform and dried \textit{in vacuo} to furnish the pure phosphorus amidite (8.5 g, 73%). A second crop (2.0 g, 18%) of product was obtained after partial removal of the solvent. The product can be recrystallized from chloroform or dichloromethane.\(^{1}\text{H-NMR (200 MHz, CDCl}_3\) \(\delta = 0.32\) (s, 3H), 1.28 (s, 3H), 2.73 (s, 3H), 2.75 (s, 3H), 4.84 (d, \(J = 8.4\) Hz, 1H), 5.20 (dd, \(J = 3.2\) Hz, \(J = 8.4\) Hz, 1H), 7.20-7.35 (m, 12H), 7.44 (d, \(J = 7.2\) Hz, 2H), 7.49 (d, \(J = 7.3\) Hz, 2H), 7.61 (d, \(J = 7.3\) Hz, 2H), 7.75 (d, \(J = 7.2\) Hz, 2H); \(^{13}\text{C-NMR (75 MHz, CDCl}_3\) \(\delta = 25.29\) (q), 35.18 (q), 35.44 (q), 81.17 (s, \(J_{PC} = 7.3\) Hz), 81.81 (s), 82.35 (d, \(J_{PC} = 23.2\) Hz), 82.45 (d), 111.71 (s), 127.09 (d), 127.25 (d), 127.64 (d), 127.65 (d), 128.07 (d), 128.67 (d), 128.74 (d), 128.95 (d), 141.77 (s), 142.09 (s), 146.43 (s), 146.85 (s); \(^{31}\text{P-NMR (80.95 MHz, CDCl}_3\) \(\delta = 139.50\).

\((1R,7R)-4-N,N-Diisopropylamino-9,9-dimethyl-2,2,6,6-tetraphenyl-3,5,8,10-tetraoxo-4-phosphabicyclo[5,3,0]decane (7.38)\)

To a stirred solution of PCl\(_3\) (360 \(\mu\)L, 4 mmol) in dry toluene (5.0 mL) under \(N_2\) at -60 to -70 \(^\circ\)C was added dropwise Et\(_3\)N (1.15 \(\mu\)L, 8 mmol) in a double Schlenk flask. After stirring for 30 min a solution of TADDOL (1.87 g, 4 mmol) in dry toluene (50 mL) was slowly added. Stirring was continued for 1.5 h and the mixture was allowed to warm to room temperature. The precipitated Et\(_3\)N.HCl salts were filtered of and the filtrate was again cooled to -60 \(^\circ\)C. Meanwhile, diisopropylamine (560 \(\mu\)L, 4 mmol) was dissolved in THF (2.5 mL) and cooled to 0 \(^\circ\)C. To this solution was slowly added BuLi (2.5 mL, 1.6 M in hexanes) and the mixture stirred for 1h after which it was cooled to -60 \(^\circ\)C. The \textit{in situ} prepared anion solution was cannulated to the phosphorus chloride solution and after 2 h stirring at -60 \(^\circ\)C the solution was allowed to warm to room temperature overnight. The conversion of the reaction was determined by \(^{31}\text{P-NMR}\) of an aliquot of the mixture and the reaction was continued until all phosphorus chloride was converted (ca.24 after starting the reaction). When the reaction was completed the solvent was evaporated and the residual oil was purified by flash chromatography (hexanes:CH\(_2\)Cl\(_2\)=1.1, \(R_f = 0.7\)) to afford 1.2 g (2.0 mmol, 50%) of a nearly colorless thick oil which could be crystallized form hexanes to yield 0.70 g (1.2 mmol, 30%) of a white solid.\(^{1}\text{H-NMR (300 MHz, CDCl}_3\) \(\delta = 0.3\) (s, 3H), 1.27 (d, \(J = 7.0\) Hz, 6H), 1.32 (d, \(J = 7.0\) Hz, 6H), 1.51 (s, 3H), 4.06 (septet, \(J = 7.0\) Hz, 2H), 4.68 (d, \(J = 8.4\) Hz, 1H), 5.27
(dd, $J = 8.4$ Hz, $J = 3.9$ Hz, 1H), 7.24-7.39 (m, 12H), 7.55 (t, $J = 8.4$ Hz, 4H), 7.70 (d, $J = 7.0$ Hz, 2H), 7.90 (d, $J = 6.6$ Hz, 2H); $^{13}$C -NMR (75 MHz, CDCl$_3$) $\delta = 24.06$ (q), 24.26 (q), 24.27 (q), 24.37 (q), 27.74 (q), 44.11 (d), 44.29 (d), 80.57 (s), 81.07 (s, $J_{PC} = 9.8$ Hz), 82.52 (d, $J_{PC} = 22.0$ Hz), 83.08 (d, $J_{PC} = 3.66$ Hz), 110.94 (s), 126.77 (d), 126.88 (d), 127.09 (d), 127.14 (d), 127.33 (d), 127.44 (d), 127.75 (d), 128.64 (d), 128.70 (d), 129.05 (d), 142.09 (s), 142.87 (s), 146.95 (s), 147.50 (s); $^{31}$P-NMR (80.95 MHz, CDCl$_3$) $\delta = 140.19$. MS(CI): 596 [M$^+$+1].

(1R,7R)-4-N,N-Dibenzy lamino-9,9-di methyl-2,2,6,6-tetraphenyl-3,5,8,10-tetraoxo-4- phosphabicyclo[5,3,0]decane (7.39)

To a stirred solution of PCl$_3$ (154 $\mu$L, 1.7 mmol) in dry toluene (2.5 mL) in a double Schlenk flask under N$_2$ at -60 to -70 °C was added dropwise Et$_3$N (495 $\mu$L, 3.4 mmol). After stirring for 30 min a solution of TADDOL (1.87 g, 1.7 mmol) in dry toluene (50 mL) was slowly added. Stirring was continued for 1.5 h and the mixture was allowed to warm to room temperature. The precipitated Et$_3$N.HCl salts were filtered of and the filtrate was again cooled to -60 °C. Meanwhile, dibenzylamine (333 $\mu$L, 1.7 mmol) was dissolved in THF (5 mL) and cooled to 0 °C and to this solution was slowly added BuLi (1.07 mL, 1.6 M in hexanes). After stirring for 0.5 h, the solution was cooled to -60 °C. The in situ prepared anion solution was cannulated to the phosphorus chloride solution and after 2 h stirring at -60 °C the solution was allowed to warm to room temperature overnight. Removal of the solvent by evaporation yielded a solid (1.0 g) from which the product was extracted with hexane using a Soxleth apparatus. After evaporation of the hexane and crystallization form MeOH:hexane the product was obtained as a white solid (340 mg, 0.5 mmol, 34%). $^{1}$H-NMR (200 MHz, CDCl$_3$) $\delta = 0.29$ (s, 3H), 1.32 (s, 3H), 4.15 (s, 2H), 4.20 (s, 2H), 4.84 (d, $J = 8.5$ Hz, 1H), 5.32 (dd, $J = 8.5$ Hz, $J = 3.4$ Hz, 1H), 7.18-7.47 (m, 16H), 7.70 (d, $J = 6.8$ Hz, 2H), 7.85 (d, $J = 8.3$ Hz, 2H); $^{13}$C -NMR (50 MHz, CDCl$_3$) $\delta = 25.17$ (q), 27.37 (q), 47.65 (t), 48.09 (t), 81.72 (d, $J_{PC} = 26.6$ Hz), 81.92 (d), 82.15 (s), 111.56 (s), 126.85 (d), 127.02 (d), 127.14 (d), 127.26 (d), 127.43 (d), 127.52 (d), 127.98 (d), 128.11 (d), 128.66 (d), 128.84 (d), 128.94 (d), 129.12 (d), 138.37 (s), 141.54 (s), 142.32 (s), 146.77 (s); $^{31}$P-NMR (80.95 MHz, CDCl$_3$) $\delta = 140.19$. MS(CI): 692 [M$^+$+1].

(1R,7R)-4-N-(1-Piperidinyl)-9,9-di methyl-2,2,6,6-tetraphenyl-3,5,8,10-tetraoxo-4- phosphabicyclo[5,3,0]decane (7.40)

To a stirred solution of PCl$_3$ (360 $\mu$L, 4 mmol) in dry toluene (5.0 mL) in a double Schlenk flask under N$_2$ at -60 to -70 °C was added dropwise Et$_3$N (1.15 mL, 8 mmol). After stirring for 30 min a solution of TADDOL (1.87 g, 4 mmol) in dry toluene (50 mL) was slowly added. Stirring was continued for 1.5 h and the mixture was allowed to warm to room temperature. The precipitated Et$_3$N.HCl salts were filtered of and the filtrate was again cooled to -70 °C. Meanwhile, piperidine (0.341 g, 4 mmol) was dissolved in THF (5 mL) the solution cooled to 0 °C and BuLi (2.5 mL, 1.6 M in hexanes) was slowly added. After
stirring for 2 h the solution was cooled to -60 °C. The in situ prepared anion solution was cannulated to the phosphorus chloride solution and after 2 h stirring at -70 °C the solution was allowed to warm to room temperature overnight. After stirring for 3 h at room temperature the solvent was evaporated and the residual solid (2.26 g) was extracted with hexane using a Soxleth apparatus. The hexane was evaporated and the residual solid was recrystallized from chloroform:hexane to yield 1.26 g of white solid (55%). $^1$H-NMR (500 MHz, CDCl$_3$) $\delta$ = 0.31 (s, 3H), 1.32 (s, 3H), 1.55-1.67 (m, 6H), 3.16-3.20 (m, 2H), 3.28-3.34 (m, 2H), 4.79 (d, $J$ = 8.5 Hz, 1H), 5.18 (dd, $J$ = 8,5 Hz, $J$ = 3.4 Hz, 1H), 7.19-7.35 (m, 12 H), 7.44 (d, $J$ = 7.5 Hz, 2H), 7.50 (d, $J$ = 7.3 Hz, 2H), 7.65 (d, $J$ = 7.5 Hz, 2H), 7.78 (d, $J$ = 7.5 Hz); $^{13}$C-NMR (50 MHz, CDCl$_3$) $\delta$ = 24.96 (t), 25.03 (q), 26.73 (t), 26.74 (t), 26.82 (t), 27.34 (q), 44.52 (t), 44.91 (t), 81.33 (s), 82.37 (d), 82.44 (d, $J_{PC}$ = 24.0 Hz), 111.34 (s), 126.87 (d), 127.01 (d), 127.08 (d), 127.24 (d), 127.35 (d), 127.50 (d), 127.01 (d), 128.60 (d), 128.70 (d), 128.89 (d), 141.83 (s), 142.17 (s), 146.52 (s), 147.05 (s); $^{31}$P-NMR (80.95 MHz, CDCl$_3$) $\delta$ = 137.39; MS(CI): 580 [M$^+$+1].

(1R,7R)-4-N,N-Dimethylamino-9-spirocyclopentyl-2,2,6,6-tetraphenyl-3,5,8,10-tetraoxo-4-phosphabicyclo[5,3,0]decane (7.41)

$\alpha,\alpha,\alpha',\alpha'$-Tetraphenyl-2-spirocyclopentyl-1,3-dioxolane-4,5-dimethanol (1.08 g, 2.0 mmol) was dissolved in dry toluene (6.0 mL) and HMPT (0.43 g, 2.6 mmol) was added dropwise under N$_2$. After stirring at reflux for 24 h the solvent was removed in vacuo. The residual solid was recrystallized from chloroform to yield 0.50 g of white solid (0.89 mmol, 45%). $^1$H-NMR (200 MHz, CDCl$_3$) $\delta$ = 0.18-0.25 (m, 1H), 0.49-0.53 (m, 2H), 1.17-1.56 (m, 4H), 1.78-1.86 (m, 2H), 2.75 (s, 3H), 2.81 (s, 3H), 4.67 (d, $J$ = 8.3 Hz, 1H), 5.22 (dd, $J$ = 8.3 Hz, $J$ = 3.4 Hz, 1H), 7.21-7.34 (m, 12H), 7.59 (t, $J$ = 8.3 Hz, 4H), 7.61 (d, $J$ = 6.6 Hz, 2H), 7.76 (dd, $J$ = 1.9 Hz, $J$ = 8.0 Hz); $^{13}$C-NMR (50 MHz, CDCl$_3$) $\delta$ = 22.00 (t), 13.06 (t), 34.60 (t), 34.94 (q), 35.33 (q), 36.28(t), 80.63 (s), 81.91 (d), 82.79 (d, $J_{PC}$ = 16.8 Hz), 120.92(s), 126.96 (d), 127.28 (d), 127.47 (d), 127.55 (d), 127.94 (d), 128.30 (d), 128.82 (d), 141.51(s), 146.95(s); $^{31}$P-NMR( 80.95 MHz, CDCl$_3$) $\delta$ = 137.39; MS(CI): 566 [M$^+$+1].

(1R,7R)-4-N,N-Dimethylamino-9,9-dimethyl-2,2,6,6-tetra-(o-methylphenyl)-3,5,8,10-tetraoxo-4-phosphabicyclo[5,3,0]decane (7.42)

$\alpha,\alpha,\alpha',\alpha'$-Tetra(o-methylphenyl)-2-spirocyclopentyl-1,3-dioxolane-4,5-dimethanol (1.0 g, 1.9 mmol) was dissolved in chloroform (5.0 mL) and HMPT (0.40 g, 2.4 mmol) was added dropwise under N$_2$. The solution was stirred at room temperature for 48 h. After removal of the solvent the residual solid that consisted of starting material and product was recrystallized from diethylether to yield 0.30 g (0.5 mmol, 25%) of white solid. A second crop of white solid could be obtained after partial evaporation of the solvent. $^1$H-NMR (300 MHz, CDCl$_3$, 80 °C) $\delta$ = 0.55 (s, 3H), 0.72 (s, 3H), 1.42 (s, 9H), 1.89 (s, 3H), 2.05 (s, 3H), 2.08 (s, 3H), 5.79 (d, $J$ = 8.5 Hz, 1H), 5.92 (d, $J$ = 8.5 Hz, 1H), 7.0-7.4 (m, 12H), 7.78-7.82 (m, 4H); due to hindered rotation at room temperature and relatively low stability in solution at elevated
temperatures no good $^{13}$C-NMR and $^{31}$P-NMR spectra could be obtained; MS(CI): 596 [M$^{+}$+1].

**Copper catalyzed conjugate addition of Et$_2$Zn to 2-cyclohexenone**

A solution of flame dried Cu(OTf)$_2$ (4.5 mg, 0.012 mmol) and chiral amidite (0.024 mmol) in toluene (5.0 mL) was stirred at ambient temperature for 1-2 h under N$_2$ atmosphere. Normally this results in a slightly turbid solution. The solution was cooled to -35 to -40 °C and 2-cyclohexenone (1.0 mmol) was added followed by slow addition of Et$_2$Zn in toluene (1.1 M, 1.5 mmol). The reaction was stirred for an additional 3 h and saturated NH$_4$Cl solution (10 mL) was added. The aqueous layer was extracted 3 times with Et$_2$O (10 mL) and the combined organic layers were dried (MgSO$_4$), the solvent partially evaporated, methanol was added and the remainder of the solvent was removed *in vacuo*. The crude product was purified by flash chromatography. The e.e. of 7.4 was determined by GC analysis on a chiral stationary phase (CHIRALPAK G-TA, 50m x 0.25mm, 100°C, $T_r$= 23.6 min (R), $T_r$= 24.8 min (S).

**Copper catalyzed conjugate addition of Et$_2$Zn to cyclopentenone**

Analogous to the general procedure of the copper catalyzed conjugate addition of Et$_2$Zn to 2-cyclohexenone, the reaction with 2-cyclopentenone was performed at -78°C and the conversion was monitored by GC analysis (HP-1, cross linked methylsilicon gum, 15m x 0.35 mm, oven temperature: 80 °C, injection temperature 200 ° C, 2-cyclopentenone: $T_r$ = 2.17 min; 7.43: $T_r$ = 4.57 min). After stirring for 3d at this temperature and a work up as described above, the product was purified by rotating disc chromatography (SiO$_2$, hexane:Et$_2$O = 1:1, R$_f$=0.5). Yield 40-58% (Caution has to be taken during the evaporation of the solvent, since 7.43 is extremely volatile!). $^1$H-NMR (200 MHz, CDCl$_3$) $\delta$ = 0.94 (t, $J$ = 7.5 Hz, 3H), 1.38-1.52 (m, 3H), 1.71-1.85 (m, 1H), 2.03-2.44 (m, 5H); $^{13}$C-NMR (50 MHz, CDCl$_3$) $\delta$ = 11.96 (q), 28.27 (t), 28.89 (t), 38.31 (t), 38.67 (d), 44.78 (t), 217. (s); GCMS: 112 [M$^+$].

**Crystal data for (1R,7R)-4-N,N-dimethylamino-9,9-dimethyl-2,2,6,6-tetraphenyl-3,5,8,10-tetraoxo-4-phosphabicyclo[5,3,0]decane (7.36)**

Colorless transparent block shaped crystals were obtained from crystallization from chloroform. The crystal of approximate dimensions of 12 x 0.15 x 0.22 mm was mounted on top of a glass fiber and transferred into the cold nitrogen cold stream of the low temperature unit mounted on an Enraf-Nonius CAD-4F diffractometer, interfaced to a INDY (Silicon

42 van Bolhuis, F. *J. Appl. Cryst.* 1971, 4, 263
44 X-ray analysis performed by A. Meetsma.

136
Graphics) UNIX computer (Mo tube, 50 kV, 40 mA, monochromated Mo-Kα radiation, Δω = 0.80 + 0.34 tg θ).

Unit cell parameters and orientation matrix were determined from a least-squares treatment of the $SET_4$ setting angles of 22 reflections in the range $12.03^\circ < θ < 20.37^\circ$. The unit cell was identified as triclinic, space group $P\bar{1}$: the $E$-statistics were indicative of a non-centrosymmetric space group. Reduced cell calculations did not indicate any higher metric lattice symmetry and examination of the final atomic coordinates of the structure did not yield extra metric symmetry elements.

The intensities of three standard reflections, monitored every 3 h of X-ray exposure time, showed no greater fluctuations during data collection than those expected from Poisson statistics. Intensity data were corrected for Lorentz and polarization effects, scale variation, but not for absorption and reduced to $F_o^2$.

The structure was solved by direct methods with $SIR97$. The positional and anisotropic thermal displacement parameters for the non-hydrogen atoms were refined. A subsequent difference Fourier synthesis resulted in the location of all the hydrogen atoms, which coordinates and isotropic thermal displacement parameters were refined. Final refinement on $F^2$ carried out by full-matrix least-squares techniques converged at $wR(F^2) = 0.0759$ or $2877$ reflections with $F_o^2 ≥ 0$ and $R(F) = 0.0338$ for $2607$ reflections with $F_o ≥ 4.0 \sigma(F_o)$ and $488$ parameters. The final difference Fourier map was essentially featureless: no significant peaks having chemical meaning above the general background were observed. The absolute structure actually chosen was determined by Flack's $x$-refinement ($x = 0.09(9)$). These absolute exhibited configuration is in agreement with the predicted configuration as known by synthesis route.

The positional and anisotropic thermal displacement parameters for the non-hydrogen atoms and isotropic thermal displacement parameters for hydrogen atoms were refined on $F^2$ with full-matrix least-squares procedures minimizing the function $Q = \sum_h [w(F_o^2 - kF_c^2)]^2$, where $w = 1/[2(F_o^2) + (aP)^2 + bP]$, $P = [\max(F_o^2,0) + 2F_c^2] / 3$, $F_o$ and $F_c$ are the observed and calculated structure factor amplitudes, respectively; $a$ and $b$ were refined. Reflections were stated observed if satisfying $F^2 > 0$ criterion of observability.

Crystal data and numerical details on data collection and refinement are given in Table 4. Final fractional atomic coordinates equivalent displacement parameters for the non-hydrogen atoms are given in Table 5. Molecular geometry data are collected in Table 6. Neutral atom

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52 Altomare, A., Cascarano, G., Giacobazzo, C., Guagliardi, A., Moliterni, A.G.G., Burla, M.C., Polidori, G., Camalli, M., Spagna, R. SIR-97. A Package for crystal structure solution by direct methods and refinement. Univ. of Bari, Univ. of Perugia and Univ. of Roma, 1997, Italy.
scattering factors and anomalous dispersion corrections were taken from *International Tables of Crystallography*. All calculations were performed on the HP9000/735 computer at the University of Groningen with the program packages *SHELXL* (least-square refinements), *PLATON* (calculation of geometric data and the *ORTEP* illustrations) and a locally modified version of the program *PLUTO* (preparation of illustrations).

**Table 4** Crystal data, data collection, structure solution, and refinement for 7.36.

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<tr>
<th>Crystal data</th>
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<tr>
<td>Chemical formula</td>
<td>C\textsubscript{33}H\textsubscript{34}NO\textsubscript{4}P</td>
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<tr>
<td>Formula weight, (g.mol(^{-1}))</td>
<td>539.61</td>
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<tr>
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<tr>
<td>Space group</td>
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<tr>
<td>(a, b, c) (Å)</td>
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<tr>
<td>(\alpha, \beta, \chi) (°)</td>
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<tr>
<td>(V, (Å\textsuperscript{3}))</td>
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<tr>
<td>(Z)</td>
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<tr>
<td>(\rho_{\text{calc}},\ g.cm\textsuperscript{-3})</td>
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<tr>
<td>(F(000),\ electrons)</td>
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<td>(\mu(Mo\ K\alpha),\ \text{cm}^{-1})</td>
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<td>Approx. crystal dimension, mm</td>
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**Data collection.**

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<td>Temperature, (K)</td>
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<tr>
<td>(\theta) range (°)</td>
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<td>Total data</td>
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<tr>
<td>Unique data</td>
<td>2877</td>
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**Refinement.**

| Number of reflections \((F_o^2 \leq 0)\) | 2877             |
| Number of refined parameters           | 488              |
| Final agreement factors:               |                  |
| \(wR(F) = \left[ \Sigma[w(F_o^2 - F_c^2)]^2 \right]^{1/2} / \Sigma[w(F_o^2)]\) | 0.0759         |
| \(R(F) = \left[ \Sigma||F_o|| - ||F_c|| \right] / \Sigma||F_o||\) | 0.0338          |

---

Table 5 Selected Interatomic Distances (Å).<sup>a</sup>

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<th>P-O(2)</th>
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<th>C(4)-C(17)</th>
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<td>P-N</td>
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<td>C(29)-C(31)</td>
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<td>1.538(5)</td>
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<td>1.511(4)</td>
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<td>1.511(4)</td>
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<sup>a</sup>Standard deviations in the last decimal place are given in parentheses.

Table 6 Selected Interatomic Bond angles (°)<sup>a</sup>

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<th>O(1)-P-O(2)</th>
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<th>O(2)-C(4)-C(17)</th>
<th>O(2)-C(4)-C(23)</th>
<th>O(2)-C(4)-C(27)</th>
<th>O(2)-C(4)-C(29)</th>
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<td>O(1)-C(1)-C(2)</td>
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<sup>a</sup>Standard deviations in the last decimal place are given in parentheses.