Chapter 3

Broadening the scope and probing the efficiency of the copper-phosphoramidite catalyzed enantioselective 1,4-addition

3.1 Introduction

In Chapter 1, the discovery of phosphoramidite L1 (Figure 3.1) in our laboratories is described. In the copper catalyzed 1,4-addition of Et₂Zn to 2-cyclohexenones, this ligand was the first to afford complete stereocontrol. Since the importance of an enantioselective catalytic process is strongly determined by its applicability in organic synthesis, we were interested in broadening further the scope of this reaction, in particular with cyclic substrates. We therefore decided to test different substrates, especially 2-cycloheptenone and 2-cyclooctenone, in the asymmetric 1,4-addition reaction. Furthermore, the efficiency of the catalyst based on (S,R,R)-L1 was examined.

3.2 Enantioselective 1,4-addition of Et₂Zn to 2-cycloalkenones

Cycloalkenones 3.1-3.3 (Figure 3.1) were tested as substrates in the enantioselective 1,4-addition of Et₂Zn under standard conditions; 1 mol% Cu(OTf)₂, 2 mol% (S,R,R)-L1, 1.2 equivalents of Et₂Zn in toluene at −30 °C.

![Figure 3.1](image-url)
2-Cyclooctenone (3.2) was synthesized in two steps by a modification of a literature procedure. Cyclooctene (3.7) was brominated at the allylic position with NBS. The resulting bromide 3.8 was directly oxidized to 2-cyclooctenone in moderate yield using bis-tetrabutylammonium dichromate (TBADC) (Scheme 3.1).

Both in the case of 2-cycloheptenone (3.1) and 2-cyclooctenone (3.2) a fast and clean reaction took place with Et₂Zn in the presence of Cu(OTf)₂ and (S,R,R)-L₁. After 1 h all starting material was converted and only the 1,4-addition products, 3.4 and 3.5 respectively, were observed by GC. Analysis of the isolated product 3.4 by chiral GC showed that the ethyl addition product was formed with 99% ee, the highest ee reported so far for this substrate (see Chapter 2). The ee of 3.5 was determined by derivatization with (2S,3S)-(+)‐2,3‐butanediol to give two diastereomeric ketals. GC analysis of these ketals showed that 3.5 was formed in 97% ee. It appears that contrary to 2-cyclopentenone, which gives only 10% ee using (S,R,R)-L₁ under the standard conditions (see Chapter 1), larger rings give a very high enantioselectivity, thus increasing the range of suitable substrates for this enantioselective 1,4-addition.

With 5,5-dimethyl-2-cyclohexenone (3.3) as the substrate, a clean conversion to the ethyl addition product 3.6 is observed after reacting overnight, as determined by GC. Compound 3.6 was isolated in 71% yield with 88% ee. Compared to the ee obtained with 2-cyclohexenone and 4,4-dimethyl-2-cyclohexenone (both >98% ee), 3.6 is formed with a somewhat lower enantioselectivity. This can tentatively be explained by assuming an unfavorable 1,3-diaxial effect in the transition state, where the steric interactions between the methyl groups and the nucleophile prevent complete enantioselection.

### 3.3 Enantioselective 1,4-addition of R₂Zn to 2,6-cycloheptadienone

Because of the high enantioselectivity in the copper-phosphoramidite catalyzed 1,4-addition of Et₂Zn to 2-cycloheptenone, we decided to study the corresponding reaction of the structurally related substrate 2,6-cycloheptadienone (3.12). From a synthetic point of view, 3.12 is an interesting substrate since its monomethyl adduct (3.13a) was used previously in the total synthesis of (+)-octalactins A (3.9) and B (3.10), marine metabolites isolated from a *Streptomyces* species. The enantioselective 1,4-addition of Me₂Zn to 3.12 could also provide...
a short route for the synthesis of clavularin B (3.11), a cytotoxic natural compound (see also Scheme 2.6 in Chapter 2).11

2,6-Cycloheptadienone (3.12) was prepared in 4 steps from cycloheptanone according to a literature procedure.12 Addition of Me₂Zn (1.2 equivalents) to 3.12 under standard conditions (Section 3.2) gave a smooth reaction allowing the isolation of (S)-3.13a in 76% yield with 99% ee, as determined by chiral GC (Scheme 3.2).13 Thus, dienone systems also are excellent substrates in the copper-phosphoramidite catalyzed asymmetric 1,4-addition, which has already been demonstrated previously for cyclohexadienones.1,14 Addition of Et₂Zn also gave a smooth reaction, reaching full conversion after 1 h. After column chromatography 3.13b was isolated in 83% yield and GC analysis showed an ee >96%.15 To the best of our knowledge, this is the first report of a (catalytic) asymmetric 1,4-addition to 3.12.

No twofold addition products were observed in the ¹H-NMR spectrum of the crude products or by GC analysis of the reaction mixture. As a matter of fact, such bisadducts are not expected to be formed, since the zinc enolate formed after the first addition is not susceptible to a second 1,4-addition under anhydrous conditions and in the absence of other possible proton donors.

The highly enantioselective 1,4-addition of Me₂Zn to 3.12 provides a convenient entry in to the synthetically important compound 3.13a by a much simpler approach than the two routes published hitherto. One of these routes comprises a 7-step synthesis starting from (+)-citronellic acid giving (R)-3.13a in 23% overall yield.9 In the other route, starting from 3.12, a diene is used as a chiral auxiliary to protect one of the double bonds by a Diels-Alder
reaction, after which a methyl cuprate addition followed by a retro Diels-Alder reaction give 3.12 with an ee of >98% in 80% overall yield.\textsuperscript{16}

### 3.4 Reducing the amount of catalyst

Apart from broadening the scope of the substrates that are applicable in the copper-phosphoramidite catalyzed enantioselective 1,4-addition, we were also interested in probing the efficiency of the catalyst prepared from \( \text{Cu(OTf)}_2 \) and \((S,R,R)-L1\). Especially the fast and clean reaction observed under standard conditions in the 1,4-addition of \( \text{Et}_2\text{Zn} \) to 2-cyclohexenone 3.14 (see Section 1.3), stimulated us to minimize the amount of catalyst necessary to obtain complete conversion and high enantioselectivity. Initial experiments showed that 0.5 mol\% \( \text{Cu(OTf)}_2 \) and 1 mol\% \((S,R,R)-L1\) were sufficient to obtain full conversion in 1 h to provide 3.15 with >98% ee.

A solution (10 ml) containing 0.0025 mmol (0.06 mol\%) \( \text{Cu(OTf)}_2 \) and 0.0050 mmol (0.12 mol\%) \((S,R,R)-L1\) in toluene/dichloromethane (see Experimental Section), was used for the enantioselective catalytic 1,4-addition of 1.5 equivalents of \( \text{Et}_2\text{Zn} \) to 0.40 ml (4.19 mmol) of 2-cyclohexenone (Scheme 3.3).

![Scheme 3.3 Catalytic enantioselective 1,4-addition to 2-cyclohexenone.](image)

The reaction was followed in time by GC analysis of samples taken after certain intervals and the turnover numbers (t.o.n. = the number of moles of product formed per mole of catalyst) were calculated (see Experimental Section for details). Figure 3.3 shows a plot of the number of turnovers to 3-ethylcyclohexanone (3.15) against time. After 15 minutes 200 turnovers were reached, \textit{i.e.} an initial turnover frequency (t.o.f.) of 800 h\textsuperscript{-1} and after 180 minutes the reaction was almost complete, having reached a t.o.n. of 1500. A duplo experiment gave 1440 t.o. after 180 minutes. Formation of other products was not observed by GC.
Noyori et al. have recently reported 10000 t.o.n. in the 1,4-addition of Et₂Zn to 3.14 using CuCN and an achiral sulfonamide ligand.\textsuperscript{17} However, a catalytic enantioselective 1,4-addition using such low catalyst loadings was not reported previously, although Pàmies et al. reported a t.o.f. of 1200 h\(^{-1}\) after 5 min of reaction using 2.5 mol\% of a chiral phosphite based copper catalyst (see Chapter 2, Section 2.2.2).\textsuperscript{18} Typically, the amounts of catalyst used in the various systems range from 0.5-5.0 mol\%.\textsuperscript{19} The ee of 3.15 obtained with the use of 0.06 mol\% Cu(OTf)\(_2\) and 0.12 mol\% (S,R,R)-L1 was 96\%, which is lower than the >98\% ee observed under the standard conditions (Section 3.2). This is probably due to a slow blank reaction, \textit{i.e.} a 1,4-addition without the involvement of (S,R,R)-L1, which produces a small amount of racemic material that slightly lowers the ee. Presumably, the catalyzed reaction in the presence of 1 mol\% of catalyst is so fast that the blank reaction has a negligible effect on the ee.

Because the reaction is still relatively fast at this low catalyst loading, we assumed that the catalyst was still active. To test this assumption, an additional 0.40 ml of 2-cyclohexenone and 1.5 equivalents of Et₂Zn were added to the reaction mixture after approximately 4 h. After reaction overnight at \(-30\) °C, GC analysis showed that the extra 2-cyclohexenone was almost completely converted to 3.15, the calculated t.o.n. being >3000. At this point the ee of the product was 95\%. These experiments clearly show that the catalyst is very active, even at low catalyst loading. Full conversions may be obtained with even lower catalyst loading, although this might result in some depletion of the enantioselectivity.
3.5 Conclusions

The copper-phosphoramidite catalyst that consists of Cu(OTf)₂ and (S,R,R)-L₁ not only gives high ee’s in the 1,4-addition of organozinc reagents to 2-cyclohexenones, but also to 2-cycloheptenone and 2-cyclooctenone. In addition, the synthetically important 2,6-cycloheptadienone (3.12) is also an excellent substrate for this catalytic system, allowing an easy entry into the building block 3.13a with 99% ee.

The amount of the copper-phosphoramidite catalyst used in the catalytic enantioselective 1,4-addition of Et₂Zn to 2-cyclohexenone can be lowered considerably and still give excellent results. The use of 0.06 mol% Cu(OTf)₂ and 0.12 mol% (S,R,R)-L₁ gave 1500 t.o. after 3 h. The only drawback is that the ee (96%) is somewhat lower using such a small amount of catalyst. The use of 0.5 mol% Cu(OTf)₂ and 1.0 mol% (S,R,R)-L₁ gives the same enantioselectivity as the use of 2.0 mol% Cu(OTf)₂ and 4.0 mol% (S,R,R)-L₁, as was reported previously.¹

The combination of the broad range of substrates tolerated by the copper-phosphoramidite catalyst containing (S,R,R)-L₁, the very high activity displayed by this catalytic system, and the availability of a variety of (functionalized) organozinc reagents, in principle makes this catalyst very suitable for applications in organic synthesis. Examples of such synthetic applications are described in the next chapters of this thesis.

3.6 Experimental section

General remarks

All solvents were reagent grade and were dried and distilled, if necessary, following standard procedures. Reagents were purchased from Acros Chimica, Aldrich, 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: δ 7.24 ppm, ¹³C: δ 77.0 ppm). Optical rotations were measured at ambient temperatures using a Perkin Elmer 241 polarimeter. Mass spectra were recorded on a AEI-MS-902 mass spectrometer by A. Kiewiet. GC measurements were performed either on 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 catalyzed 1,4-addition with the use of 2 mol% of Cu(OTf)₂ and 4 mol% of (rac)-3.16 in toluene at 0 °C.
All catalytic enantioselective 1,4-addition experiments were performed in flame dried Schlenk vessels under argon in toluene distilled from and stored over sodium (wire) under nitrogen. Both 2-cyclohexenone (3.14) and 2-cycloheptenone (3.1) were purchased from Aldrich or Fluka and distilled prior to use whereas 3-bromo-1-cyclooctene (3.8), bis-tetrabutylammonium dichromate (TBADC) and 2,6-cycloheptadienone (3.12) were prepared according to literature procedures. R. Imbos kindly provided 5,5-dimethyl-2-cyclohexenone (3.3) for which she is gratefully acknowledged.

**2-Cycloocten-1-one (3.2)**

3-Bromo-1-cyclooctene (3.8) (4.5 g, 23.8 mmol) and TBADC (15.8 g, 25 mmol) were dissolved in 150 ml of chloroform and the reaction mixture was refluxed for 2 h. The chloroform was removed in vacuo and Celite® was added to the resulting black oil until a solid mass was formed. The solid mass was transferred to a glass filter and thoroughly extracted with diethyl ether (250 ml). The combined extracts were dried over Na₂SO₄, filtered and concentrated to give crude 3.2 which was purified by bulb-to-bulb distillation (14 mmHg, 89 °C) giving 3.2 (1.2 g, 9.8 mmol, 41 %) as a colorless oil. ¹H-NMR (300 MHz, CDCl₃): δ 1.4-1.6 (m, 4H), 1.6-1.8 (m, 2H), 2.4 (m, 2H), 2.55 (dd, J = 6.6 Hz, 2H), 5.90 (d, J = 12.5 Hz, 1H), 6.2-6.3 (m, 1H). ¹³C-NMR (300MHz, CDCl₃): δ 22.55 (t), 23.06 (t), 25.10 (t), 28.53 (t), 42.70 (t), 132.37 (d), 141.61 (d), 206.05 (s).

**Enantioselective 1,4-addition of Et₂Zn to 2-cycloheptenone: 3-ethylcycloheptanone (3.4)**

Cu(OTf)₂ (3.3 mg, 0.009 mmol) and (S,R,R)-L₁ (9.7 mg, 0.018 mmol) were dissolved in toluene (10 ml) and stirred for 1 h at room temperature. The resulting colorless solution was cooled to −30 °C and 2-cycloheptenone (0.10 ml, 0.90 mmol) was added. After stirring for an additional 10 min Et₂Zn (1.0 ml of a 1.1 M solution in toluene, 1.1 mmol) was added dropwise to the colorless solution to form a bright yellow solution. Upon stirring for 1 h at −30 °C the reaction mixture turned colorless again and GC analysis on a DB-1 (J&W) column showed complete conversion of the 2-cycloheptenone. The reaction mixture was quenched with saturated aqueous NH₄Cl (10 ml) and extracted with diethyl ether (3 × 10 ml). The combined organic layers were washed with brine, dried over Na₂SO₄, and filtered. After removal of the diethyl ether, methanol (~ 30 ml) was added for azeotropic removal of the toluene and the solution was further concentrated to give crude product 3.4, which was purified by column chromatography (SiO₂, hexanes:ether 3:1) to give 3.4 (101 mg, 0.72 mmol, 80%) as a colorless oil. ¹H-NMR (300 MHz, CDCl₃): δ 0.78 (t, J = 7.3 Hz, 3H), 1.2 (m, 4H), 1.5 (m, 2H), 1.8 (m, 3H), 2.3 (m, 4H). ¹³C-NMR (300MHz, CDCl₃): δ 11.34 (q), 24.37 (t), 28.50 (t), 206.05 (s).
30.00 (t), 36.41 (t), 37.63 (d), 43.86 (t), 49.55 (t), 214, 74 (s). An ee of 99% was determined by chiral GC on a CP-cyclodex B 236 N column, 50 m × 0.25 mm, He-flow: 1.0 ml/min, 100 °C isothermic, \( t_{\text{ret}} \) 44.2 min (major enantiomer 3.4), \( t_{\text{ret}} \) 45.6 min (minor enantiomer 3.4).

3-Ethylcyclooctanone (3.5)
The enantioselective 1,4-addition of Et₂Zn to 2-cyclooctenone (3.2) (0.10 ml, 0.65 mmol) was performed under analogous conditions as described for 2-cycloheptenone (vide supra). Purification by column chromatography (SiO₂, hexanes:ether 3:1) gave 3.5 (83 mg, 0.54 mmol, 83%) as a colorless oil. 1H-NMR (300 MHz, CDCl₃): δ 0.80 (t, \( J = 7.3 \) Hz, 3H), 1.0-1.9 (m, 11H), 2.2-2.4 (m, 4H). 13C-NMR (300MHz, CDCl₃): δ 11.58 (q), 23.72 (t), 24.61 (t), 27.65 (t), 29.96 (t), 32.96 (t), 39.66 (d), 46.89 (t), 217.47 (s).

The ee of 3.5 was determined by derivatization with (2\( S \),3\( S \))-(-)-2,3-butanediol: 3-Ethylcyclooctanone (50 mg, 0.32 mmol) and (2\( S \),3\( S \))-(-)-2,3-butanediol (73 mg, 0.81 mmol) and \( p \)-toluenesulfonic acid (5 mg) were dissolved in toluene and refluxed overnight in the presence of 4 Å molecular sieves. The reaction mixture was quenched with 5% aqueous NaHCO₃ (3 ml) and extracted with diethyl ether. The combined organic layers were washed with brine, dried over Na₂SO₄, filtered and the solvents evaporated. A sample of the crude ketal was injected in to a CP-cyclodex B 236 N column, 50 m × 0.25 mm, He-flow: 1.0 ml/min, 150 °C isothermic, \( t_{\text{ret}} \) 16.9 min (major diastereomer), \( t_{\text{ret}} \) 17.3 min (minor diastereomer) indicating 97% ee. No unreacted 3.5 was observed by GC analysis.

5-Ethyl-3,3-dimethylcyclohexanone (3.6)
The enantioselective 1,4-addition of Et₂Zn to 2-cyclohexenone (3.3) (200 mg, 1.61 mmol) was performed under analogous conditions as described for 2-cycloheptenone (vide supra). Purification by column chromatography (SiO₂, hexanes:ether 4:1) gave 3.6 (176 mg, 1.14 mmol, 71%) as a colorless oil. 1H-NMR (300 MHz, CDCl₃): δ 0.98 (s, 3H), 1.1-1.4 (m, 3H), 1.5 (m, 1H), 1.5-1.8 (m, 2H), 1.9-2.1 (m, 2H), 2.3 (m, 1H). 13C-NMR (300MHz, CDCl₃): δ 202.91 (s). MS(CI) for C₈H₁₂O: m/z = 142 (M + NH₄)⁺. An ee of 88% was determined by chiral GC on a Chiraldex G-TA column, 50 m × 0.25 mm, 120 °C isothermic, \( t_{\text{ret}} \) 15.2 min (major enantiomer 3.6), \( t_{\text{ret}} \) 17.2 min (minor enantiomer 3.6).

(S)-6-Methyl-2-cyclohepten-1-one (3.13a)
The enantioselective 1,4-addition of Me₂Zn to 2,6-cycloheptadienone (3.12) (321 mg, 3.00 mmol) was performed overnight under similar conditions as described for 2-cycloheptenone (vide supra). Purification by column chromatography (SiO₂, hexanes:ether 4:1) gave (S)-3.13a (283 mg, 2.28 mmol, 76%) as a colorless oil. [\( \alpha \)]\text{D}\text{0} = -46.3° (c = 1.11, CHCl₃), lit.: [\( \alpha \)]\text{D}\text{0} = -59° (c = 1.0, CHCl₃).²² 1H-NMR (300 MHz, CDCl₃): δ 0.91 (d, \( J = 6.6 \) Hz, 3H), 1.4 (m, 1H), 1.8 (m, 1H), 2.0 (m, 1H), 2.2-2.5 (m, 3H), 2.6 (m, 1H), 5.88 (d, \( J = 12.1 \) Hz, 1H), 6.5 (m, 1H). 13C-NMR (300MHz, CDCl₃): δ 21.87 (q), 28.20 (t), 28.36 (d), 34.72 (t), 51.24 (t), 132.56 (d), 147.29 (d), 202.91 (s). MS(Cl) for C₈H₁₂O: m/z = 142 (M + NH₄)⁺. An ee of 99% was determined by chiral GC on a Chiraldex B-TA column, 30 m × 0.25 mm, He-flow: 1.0 ml/min, initial temp:
75 °C, initial time: 10 min, rate: 10 °C/min, final temp: 150 °C, t$_{\text{ret}}$ 17.1 min (S)-3.13a, t$_{\text{ret}}$ 17.2 min (S)-3.13a).

6-Ethyl-2-cyclohepten-1-one (3.13b)
The enantioselective 1,4-addition of Et$_2$Zn to 2,6-cycloheptadienone 3.12 (102 mg, 0.94 mmol) was performed under similar conditions as described for 2-cycloheptenone (vide supra). Purification by column chromatography (SiO$_2$, hexanes:ether 4:1) gave 3.13b (107 mg, 0.78 mmol, 83%) as a colorless oil. $\left[\alpha\right]_D = -54.3^\circ$ (c = 0.63, CHCl$_3$). $^1$H-NMR (300 MHz, CDCl$_3$): $\delta$ 0.86 (t, $J$ = 7.3 Hz, 3H), 1.2-1.4 (m, 2H), 1.5 (m, 1H), 1.7-1.8 (m, 1H), 1.8-1.9 (m, 1H), 2.2-2.5 (m, 3H), 2.6-2.7 (m, 1H), 5.94 (d, $J$ = 12.1 Hz, 1H), 6.6 (m, 1H). $^{13}$C-NMR (300MHz, CDCl$_3$): $\delta$ 11.70 (q), 28.37 (t), 28.87 (t), 32.54 (t), 35.10 (d), 49.15 (t), 132.80 (d), 147.41 (d), 203.44 (s). MS(Cl) for C$_9$H$_{14}$O: m/z = 156 (M + NH$_4$)+. An ee of >96% was determined by chiral GC on a Chiraldex A-TA column, 50 m × 0.25 mm, He-flow: 1.0 ml/min, 85 °C isothermic, t$_{\text{ret}}$ 39.5 min (minor enantiomer 3.13b), t$_{\text{ret}}$ 40.6 min (major enantiomer 3.13b).

Catalytic enantioselective 1,4-addition of Et$_2$Zn to 2-cyclohexenone using 0.06 mol% Cu(OTf)$_2$ and 0.13 mol% (S,R,R)-L1
Cu(OTf)$_2$ (4.7 mg, 0.0125 mmol) and (S,R,R)-L1 (13.5 mg, 0.0250 mmol) were dissolved in a mixture of freshly distilled toluene (8.0 ml) and dichloromethane (2.0 ml) and vigorously stirred for 1 h.$^{20}$ From the resulting colorless homogeneous solution 2.0 ml was transferred to a second Schlenk vessel via a syringe. The catalyst solution was diluted with toluene (8.0 ml) and stirred for 1 h. After 2-cyclohexenone (400 µl, 4.19 mmol) and n-decane (0.20 ml, 1.0 mmol, internal standard) were added the solution was cooled to −30 °C. A sample (0.1 ml) was taken (t=0) and diluted with 1 ml of diethyl ether saturated with water. This solution was filtered through a small plug of silica gel and the plug was rinsed with diethyl ether saturated with water (3 × 1 ml). Et$_2$Zn (5.7 ml of a 1.1 M solution in toluene, 6.3 mmol) was added dropwise in 1 min. Samples were taken from the reaction mixture after 15, 30, 60, 120 and 180 minutes and treated as the t=0 sample (see Figure 3.3 for results). The samples were analyzed a HP-1 dimethylpolysiloxane column. Calibration was performed using authentic samples of 2-cyclohexenone and 3-ethylcyclohexanone. T.o.n. were calculated using the Chemstation software. After 180 min, an ee of 96% was determined by chiral GC on a Chiraldex G-TA column, 50 m × 0.25 mm, He-flow: 1.0 ml/min, 110 °C isothermic, t$_{\text{ret}}$ 18.8 min ((R)-3.15), t$_{\text{ret}}$ 19.3 min ((S)-3.15).

Acknowledgements

Richard Jagt is gratefully acknowledged for performing the catalytic enantioselective 1,4-addition of Me$_2$Zn to 3.12.
3.7 References and notes

6 The ee of 3.5 using identical reaction conditions was previously incorrectly reported to be 53%.¹
15 The peaks of the two enantiomers were not completely baseline separated.
20 Dichloromethane was added to make the stock solution completely homogeneous. If toluene is used as the only solvent the solution remains a little turbid, thus hampering accurate dilution of the stock solution.