Catalytic enantioselective conjugate addition of organometallic reagents

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Chapter 4

(+)-Camphor-Derived Tri- and Tetradentate Amino Alcohols; Synthesis and Application as Ligands in the Nickel Catalysed Enantioselective Conjugate Addition of Diethylzinc

4.1 Introduction

In the previous Chapter we have seen that the conjugate addition of diethylzinc to chalcone is effectively catalysed by chiral nickel complexes derived from (-)-DAIB and (+)-DAB. Although the nature of the catalytically active complex is unknown, a mechanism has been proposed which could account for the enantioselective alkyl transfer. Probably a nickel complex with two coordinated amino alcohol ligands is involved in the rate determining step of the catalytic process. However, it should be emphasised that participation of multinuclear aggregates, consisting of nickel and zinc centers and several chiral ligands, can not be excluded. Furthermore, the nickel / amino alcohol catalysed conjugate addition of diethylzinc was only enantioselective for acyclic enones i.e. chalcones. Alkyl transfer from diethylzinc to cyclohexenone proceeded smoothly, presumably via a kinetically favoured complex or aggregate incapable of inducing enantioselectivity.

This Chapter describes attempts to isolate a mononuclear nickel complex derived of Ni(acac)_2 and two equivalents of (-)-DAIB (or (+)-DAB). Furthermore, to develop a catalyst capable of enantioselective conjugate addition of dialkylzinc reagents to cyclic and acyclic enones, several novel tri- and tetradentate tertiary amino alcohols, all derived of (+)-camphor, were synthesised. Probably the rigidity of the in situ prepared catalyst will be enhanced with these multidentate ligands, minimalising the number of possible aggregates and as a result inducing enantioselectivity for both types of substrates.

Crystallisation experiments
Synthesis, isolation, and characterisation of cis-complex 4.2 (Eq. 4.1) or the trans coordinated complex by a X-ray structure determination should give information about the complex, generated in situ in the catalytic process. Therefore, a solution of Ni(acac)_2 and 2 equivalents of (-)-DAIB (4.1) in acetonitrile was heated at reflux for 2 h and cooled slowly in an attempt to obtain crystals suitable for X-ray analysis. No crystals were formed after 1 week at -20°C and slow evaporation of the solvent did not furnish suitable material as well. Unfortunately, in toluene or with NiBr_2 instead of Ni(acac)_2, only green powders were collected. ^1H NMR measurements on these
materials in CD,CN revealed no changes in chemical shifts compared to the free ligand. Also the UV spectrum of the presumed Ni(acac),-ligand complex gave the same absorption maxima as observed for the ligand spectrum, indicating no ligand exchange under these conditions. Probably deprotonation of the alcohol group of 4.1 is required to achieve complexation of 4.1 to nickel. However, the use of Et,N, NH₃, NaOH, or NaH did not furnish material suitable for crystal structure determination or Ni(acac)₂ was isolated.

\[
\text{2} \quad \text{Ni(acac)} \quad \text{4.1} \quad \text{4.2} \quad (4.1)
\]

When the nickel catalysed conjugate addition reactions, described in Chapter 3, were performed, a slight excess of diethylzinc was used. Probably the chiral amino alcohol is deprotonated by diethylzinc forming a LZn-alkyl complex whereupon complexation to the nickel center and successive 1,4-addition can occur. Therefore, a clear solution of (-)-DAIB (or stereoisomer (+)-DAB) in acetonitrile was treated with 1 equivalent of diethylzinc (1.1M in toluene) resulting in a turbid white mixture, which was cooled with ice and quenched with 0.5 equivalent of Ni(acac)₂. Gas evolved and the mixture immediately turned red brown, indicating the formation of a nickel complex. The clear solution was allowed to stand for 3 days at room temperature, resulting in an orange precipitate. The H NMR spectrum of the precipitate showed broad signals. Unfortunately, recrystallisation of the precipitate from toluene / acetonitrile did not give crystals suitable for X-ray analysis. Possibly other geometries of the prepared nickel-ligand complex (trans coordination of two amino alcohol ligands is also possible) and larger aggregates are present as well.
4.2 Synthesis of (+)-camphor-derived tri- and tetradeutate amino alcohols

Tetradeutate amino alcohols

In order to minimalise the possible geometries of the in situ prepared nickel-ligand complexes, we were interested in the development of alkyl bridged aminoisoborneols furnishing tetradeutate ligands of type 4.3 (Eq. 4.2). Several attempts to synthesise alkyl bridged aminoisoborneols by straightforward coupling of N-methyl-3-aminoisoborneol ((+)-MAIB) (4.1b) with 1,3-dibromopropane or 1,4-dibromobutane failed, probably due to steric hindrance. Corresponding tertiary amino alcohols were only synthesised by using the primary amino alcohol and dibromoalkanes using the favoured intramolecular second substitution (see also Section 3.3). Therefore, other routes had to be developed.

Allylic and benzylic substrates undergo nucleophilic substitution especially easily, owing to resonance stabilisation of the transition state. Reaction of (+)-MAIB with the double allylic substrate (E)-1,4-dibromo-2-butene under the conditions given in equation 4.3, furnished the coupled ligand 4.3a in a moderate isolated yield (42%). Unfortunately, reduction of the double bond in compound 4.3a with hydrogen in the presence of Pd/C, resulted in a mixture of compounds. We were not able to isolated the desired compound from this mixture.

\[ \text{Reactivity of (+)-MAIB with the double benzylic substrate } \alpha,\alpha'-\text{dibromo-}m\text{-xylene under} \]
the same conditions as given in Eq. 4.3 also gave a coupled tetradentate product. However, no pure material was obtained after attempts of purification (column chromatography and crystallisation). Since these two bisallylic compounds did not give satisfactory results and other bisallylic halides are not readily available, another procedure for achieving tetradentate ligands was desirable. Secondary and tertiary amines can also be obtained via reductive amination of carbonyl compounds. At pH 6-7 the reduction of aldehydes and ketones with NaBH₄CN is negligible whereas in this pH range the reduction of the iminium group (i.e., >C=N⁺R₂ or >C=N⁺HR) proceeds smoothly resulting in the corresponding amine.⁴ Although the presence of water hampers the initial iminium formation, a commercially available solution of glutaric dialdehyde in water (25 wt%) was used in a double reductive amination with primary amine 4.1a (Eq. 4.4).⁵ Remarkably, only tertiary amine 4.4 was formed in a relatively good yield (50%). This indicates the large rate difference between the intramolecular iminium formation of a secondary amine and the intermolecular iminium formation of a primary amine, in favour of the sterically more hindered intramolecular reaction.

![Chemical reaction diagram](image)

Although this intramolecular reaction might be suppressed by using a large excess of the amine,⁶ it also suggested the possibility to use the sterically hindered secondary amine (+)-MAIB (4.1b). Reaction of glutaric dialdehyde with two equivalents of 4.1b, however, furnished the double oxazolidine 4.5 in a 60% isolated yield (Eq. 4.5). Again an intramolecular reaction, i.e. the nucleophilic addition of the alcohol moiety to the imino intermediate, is much faster than a intermolecular reduction of the latter compound.
The acetal carbon-oxygen bond of an oxazolidine can be cleaved by reduction with LiAlH₄, leading to an N-substituted amino alcohol. However, treatment of compound 4.5 with an excess of LiAlH₄ in ether, dioxane, or THF resulted in unreacted starting material, a mixture of unidentified compounds, and products due to cleavage of the acetal carbon-nitrogen bond, respectively.

When (+)-MAIB was protected with trimethylsilyl chloride and coupled subsequently with glutaric dialdehyde under the conditions given in Eq. 4.5, again the double oxazolidine 4.5 was detected in the crude product. From these results it was clear that we had to turn to an alternative procedure to achieve tetradentate amino alcohol ligands.

Properly speaking, the direct N-alkylation of secondary amino alcohols 4.1b or 4.8 is the only versatile option and therefore this procedure was reinvestigated. The nucleophilic substitution of the secondary amine (+)-MAIB (4.1b) to alkyl halides other than methyl iodide does not proceed in refluxing ethanol, ethyl acetate, or DMF under basic conditions (see also Section 3.3). More promising results were achieved when stereoisomer N-methyl-3-aminoborneol ((+)-MAB, 4.8), synthesised and purified according to a literature procedure, was used as nucleophile in the coupling reaction with dibromoalkanes. Apparently, the endo stereoisomer is somewhat less sterically demanding and therefore better accessible for alkyl halides. In refluxing acetonitrile and in the presence of one equivalent K₂CO₃, tetradentate amino alcohols 4.9a and 4.9b were synthesised and isolated in remarkable high yields (ca. 80%, Scheme 4.1). This substitution reaction was not successful with 1,4-dibromobutane as alkylating reagent. Probably the nucleophilic substitution in the former cases is assisted by neighboring groups. Under these optimised conditions other sterically hindered (intramolecular) N,N-alkylations were performed in good yields as well (see for example Section 3.3).
Scheme 4.1 Synthesis of tetradeinate amino alcohols 4.9. (a) diethyl carbonate, K$_2$CO$_3$, reflux (50%) (b) LiAlH$_4$, THF, reflux (95%) (c) 1,2-dibromoethane or 1,3-dibromopropane, K$_2$CO$_3$, acetonitrile, reflux (80%).

With tetradeinate ligand 4.9b the corresponding crystallisation experiments as described above for bidentate ligand 4.1 were performed. So, when a mixture of 4.9b in acetonitrile / toluene was treated with two equivalents of diethylzinc (1.1M in toluene) a clear yellow solution was obtained and gas evolved (probably ethane). Next, one equivalent of Ni(acac)$_2$ was added resulting in a clear green solution. The colour of the solution changed slowly (in 1 h) to orange. Upon standing at room temperature no solid material was obtained; slow diffusion of diethyl ether into the mixture did not give satisfactory results either. All further attempts to isolate crystals suitable for X-ray analysis were not successful, so far.

Tridentate amino alcohols
For comparison two novel tridentate amino alcohols, both derived of (+)-camphor were synthesised. Since Tanaka and co-workers achieved very high e.e.'s (> 90%) in the enantioselective conjugate addition of methylolithium to a cyclic enone mediated (or catalysed) by a copper complex of methylpyrrole substituted aminoborneol 4.10$^{7,8}$ (see Section 2.4), we were interested in the behaviour of this secondary amine and the corresponding tertiary amine compound in the nickel catalysed conjugate addition of diethylzinc. Therefore, compound 4.10 was synthesised according to the literature
procedure and subsequently N-methylated with an excess of methyl iodide (Scheme 4.2).

Scheme 4.2 Synthesis of amino alcohols 4.10 and 4.11. (a) i. 1-methylpyrrole-2-carboxaldehyde, Na$_2$SO$_4$, dichloromethane. ii. LiAlH$_4$, diethyl ether (45%). (b) excess MeI, NaOH, diethyl ether, water (83%).

Due to the aromaticity of pyrrole, the electron pair on the nitrogen of the pyrrole group is hardly accessible for metal complexation. However, the synthesis of the better coordinating pyridine substituted analogous amino alcohol 4.12, by employing pyridine-2-carboxaldehyde, failed (conditions as in Scheme 4.2); the pyridine group was N-methylated as well in the last step. Fortunately, a second route to the pyridine substituted amino alcohol using secondary amine 4.8 and 2-picolyl chloride hydrochloride furnished the desired tridentate ligand 4.12 in 75% yield (Eq. 4.6).

The enantiomeric purity of all novel tri- and tetradsentate ligands was not determined, but on the basis of the reaction conditions used no epimerisation (or racemisation) is expected. Furthermore, (-)-DAIB (4.1) and compound 3.5e, synthesised via analogous procedures, proved to be enantiomerically pure, as described in Section 3.3.
4.3 (+)-Camphor-derived tri- and tetradsentate $\beta$-amino alcohols as chiral ligands in the nickel catalysed addition of diethylzinc to chalcone 6 cyclohexenone

Chalcone as substrate
With the chiral ligands described in the previous Section, we examined the effect of additional coordinating groups on the enantioselectivity in the nickel catalysed addition of diethylzinc to chalcone. The results are summarised in Table 4.1. Ligand 4.3a, containing a bridge with a double bond, gave 1,4-product 4.14 with 49% e.e., which is lower than found with two equivalents of the corresponding bidentate ligand 4.1 (65% e.e., see Section 3.4). Possibly the trans olefinic bond prevents coordination of both amino alcohol moieties in ligand 4.3a to the nickel center, resulting in less enantioselective catalysis. In Chapter 3 it was already shown that at least two equivalents of bidentate amino alcohols are required for high enantioselectivities.
Table 4.1 (+)-Camphor derived amino alcohol compounds as ligand in the nickel catalysed enantioselective conjugate addition of diethylzinc to chalcone (4.13).a

![Chemical Structure](image)

<table>
<thead>
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<th>entry</th>
<th>chiral ligand (mol%)</th>
<th>yield (%)b</th>
<th>e.e. (%)c</th>
<th>abs. conf.d</th>
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<td>49</td>
<td>R</td>
</tr>
<tr>
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<td>4.5 (8)</td>
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<td>R</td>
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<td>21</td>
<td>S</td>
</tr>
<tr>
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<td>4.9b (8)</td>
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<td>69</td>
<td>S</td>
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<td>S</td>
</tr>
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<td>83</td>
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<tr>
<td>10</td>
<td>4.16 (16)</td>
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</table>

*Reactions at -25°C in 2 ml of acetonitrile using an in situ prepared catalyst from 7 mol% Ni(acac) and given amount of chiral ligand. 1.5 Equivalent of diethylzinc in toluene (1.1M) was used (unless stated otherwise). Reaction time 16 h. b. Isolated yield of the 1,4-product. c. Determined by HPLC analysis. (see Chapter 3) d. Comparison of retention times of 4.14 with known data gave the absolute configuration. e. Diethylzinc in hexane (0.9M) was used.

From the results found with the double oxazolidine 4.5 it is obvious that a free alcohol function must be present. Although diethylzinc is activated by the oxazolidine, no enantioselectivity was observed. With the alkyl bridged ligands 4.9a and 4.9b alternating e.e. values for 4.14 were obtained, compared to the e.e. value found with two equivalents of the corresponding bidentate ligand 4.15 (82% e.e., Section 3.4). Probably somewhat different aggregates are formed in solution, especially with ligand 4.9a, resulting in less enantioselective alkyl transfer. Compound 4.9 prohibits trans coordination of both amino alcohol moieties by the alkyl bridge, which may be another explanation for the observed decrease in enantioselectivity.
When the secondary amino alcohol 4.10 was employed as chiral ligand a remarkable high enantioselectivity (57% e.e.) has been determined for 1,4-product 4.14. In Chapter 3 primary and secondary amino alcohols were also used as ligand, however, no enantioselectivity was observed. In spite of the proposed structure, responsible for the highly enantioselective alkyl transfer found by Tanaka, where coordination of the pyrrole group is totally ignored, the role of the pyrrole group in this alkyl transfer can not be excluded. However, it is possible that only steric effects of the pyrrole group are responsible for the enantioselectivity found. Furthermore, it should be emphasised that in these experiments the diethylzinc is added as solution in toluene instead of the formerly used hexane solution. In comparison, when aminoborneol (+)-DAB was employed as chiral ligand, the change of co-solvent resulted in a minor enhancement of the e.e. found for 4.14 (82% vs. 87% e.e.).

With the tertiary amine ligand 4.11, enantioselectivities for 4.14 were observed which are comparable with those found for (+)-DAB (4.15) (entries 6-8). An interesting feature of 4.11 is that even with a ligand-to-nickel ratio of 1 a significant e.e. value of 65% was found, indicating a role of the pyrrole moiety (vide supra).

Rather to our surprise the pyridine substituted ligand 4.12 furnished the 1,4-product with no enantioselectivity at all (entry 9). Most probably, only the pyridine group is involved as a coordinating group in the in situ preparation of the catalyst, resulting in a complex or aggregate with the chiral backbone too far away from the active center. To compare this remarkable result, bidentate ligand 4.16, synthesised by nucleophilic addition of monolithiated 2,6-lutidine to (+)-camphor, was tested as ligand in the nickel catalysed conjugate addition of diethylzinc to 4.13. Again no enantioselectivity was found with this pyridine substituted ligand (entry 10). Although ligand 4.16 is a γ-pyridine alcohol instead of a β-amino alcohol as all other ligands, the pyridine entity seems to be detrimental to asymmetric induction in this conjugate addition reaction.

All novel tri- and tetradentate amino alcohols furnished the same enantiomer of 4.14 in excess as compared to the results found for the analogous bidentate ligands (see Chapter 3), indicating that the direction of asymmetric induction is not influenced by introducing additional coordinating and / or sterically demanding entities.
Cyclohexenone as substrate
As shown above the tri- and tetradeinate ligands were able to induce asymmetric ethyl transfer to chalcone. In order to investigate whether this enantioselective alkyl transfer can also be achieved with cyclic substrates, compounds 4.9-4.12 and 4.16 were examined as chiral ligands in the conjugate addition of diethylzinc to cyclohexenone (4.17). The results are summarised in Table 4.2.

Table 4.2 Amino alcohols 4.9-4.12 and 4.16 as chiral ligand in the Ni(acac)\textsubscript{2} catalysed 1,4-addition of diethylzinc to cyclohexenone.\textsuperscript{a}

<table>
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<th>abs. conf.\textsuperscript{c}</th>
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<td>~ 0</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>4.9b (8)</td>
<td>~ 0</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>4.10 (16)</td>
<td>7</td>
<td>S</td>
</tr>
<tr>
<td>4</td>
<td>4.11 (16)</td>
<td>12</td>
<td>S</td>
</tr>
<tr>
<td>5</td>
<td>4.12 (16)</td>
<td>~ 0</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>4.16 (16)</td>
<td>20</td>
<td>R</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Reactions at -25°C in 2 ml of acetonitrile using in situ prepared catalyst from 7 mol% Ni(acac)\textsubscript{2} and given amount of chiral ligand. 1.5 Equivalent of diethylzinc in toluene (1.1M) was used. Reaction time 16 h.

\textsuperscript{b} Conversion to the 1,4-product > 90% as determined by GC analysis. Isolated yields of 3-ethylcyclohexanone (4.18) > 70%.

\textsuperscript{c} Enantiomeric excess of 4.18 was determined by derivatisation with optically pure 1,2-diphenylethylene diamine. Comparison of the optical rotation of 4.18 with known data gave the absolute configuration (see Chapter 5).

In all cases the 1,4-product 4.18 was isolated in good yields (> 70%). However, with tetradeinate ligand 4.9 no enantioselectivity was observed, and tridentate ligands 4.10 and 4.11 were not able to induce selectivity exceeding 12% e.e. (for ligand 4.11). The pyridine substituted tridentate ligand 4.12 gave no enantioselectivity, whereas bidentate ligand 4.16 furnished 1,4-product 4.18 with an e.e. of 20%. Remarkably, the
ligands 4.10 and 4.11 furnished the S enantiomer of 4.18 in slight excess. This is the enantiomer found as product in the reaction with chalcone (s-cis enone), indicating that with cyclohexenone (s-trans enone) another aggregate, present in solution, is responsible for the enantioselective alkyl transfer.

4.4 Summary and concluding remarks

In this Chapter the synthesis of several novel tri- and tetradaentate amino alcohols, all derived from (+)-camphor, have been described. The initial attempt to synthesise N-alkylated amino alcohols by reductive amination was hampered by intramolecular reaction with the alcohol moiety. Although the N,N-dialkylations were hindered by the sterically demanding backbone, successful procedures for the synthesis of tertiary amines were developed by using reactive alkyl halides in refluxing acetonitrile. Unfortunately, crystallisation experiments of the complexes of these multidentate ligands and the corresponding bidentate ligands with nickel were unsuccessful so far. Catalytic enantioselective conjugate additions of diethylzinc, employing the tetra- and tridentate amino alcohols were successful with chalcone as substrate. About the same enantioselectivities were achieved compared to the corresponding bidentate ligands. In contrast to the results described in Chapter 3, the secondary amino alcohol 4.10 was successful as a chiral ligand in the enantioselective conjugate addition of diethylzinc to chalcone. Apparently, sterically demanding substituents on the amine entity are crucial for enantioselective catalytic conjugate addition reactions and the most exciting ligand still has to be prepared. Remarkably, the tridentate ligand with a pyridine substituent furnished the 1,4-product without any enantioselectivity, indicating the very specific ligand requirements.

Unfortunately, the initial goal to develop a catalytic system, capable of enantioselective conjugate addition of diethylzinc to both cyclic and acyclic substrates, failed. With cyclohexenone as substrate good yields of 1,4-product were isolated, however, e.e.'s were not exceeding 20%. Therefore other catalytic systems, derived from other metal salts and chiral ligands, seem to have more potency.

4.5 Experimental section

For general remarks, see Section 3.8.

Materials
The following compounds were commercially available and used without further
purification: (E)-1,4-dibromo-2-butene (Aldrich), α,α'-dibromo-m-xylene (Aldrich), glutaric dialdehyde (25 wt% in water, Aldrich), NaBH₃CN (Aldrich), 1-methylpyrrole-2-carboxaldehyde (Aldrich), 2-pyridinecarboxaldehyde (Aldrich), 2-picoly1 chloride hydrochloride (Aldrich). For the synthesis of compounds 4.1, 4.1a, 4.1b, 4.6 and 4.15 see Chapter 3. (+)-Cis-end0-N-[(1-methylpyrrol-2-yl)methyl]-3-aminoborne0l (4.10) was synthesised according to a literature procedure.

For all other materials, see Section 3.8.

Attempted synthesis of N,N'-Bis[3-cis-exo-isoborneol]-N,N'-dimethyl-1,4-diamino-2-butene (general procedure for 4.3)

A mixture of cis-exo-N-monomethyl-3-aminoisoborneol ((+)-MAIB, 4.1b) (0.367 g, 2.0 mmol), 1,m-dibromoalkane (1.0 mmol) and K₂CO₃ (0.276 g, 2.0 mmol) in 50 ml of ethanol (ethyl acetate or DMF) was stirred and refluxed for 1 week. The mixture was poured into 25 ml of H₂O and extracted with CH₂Cl₂ (3 x 30 ml). The combined organic layers were washed with brine (50 ml) and dried (Na₂SO₄). Filtration and evaporation of the solvent gave a crude oil that showed several spots on TLC (SiO₂ CHCl₃/methanol (4:1)). We were not able to isolate the desired product from this mixture.

(-)-(E)-N,N'-Bis[3-cis-exo-isoborneol]-N,N'-dimethyl-1,4-diamino-2-butene (4.3a)

A mixture of cis-exo-N-monomethyl-3-aminoisoborneol ((+)-MAIB) (4.1b) (0.446 g, 2.43 mmol), (E)-1,4-dibromo-2-butene (0.260 g, 1.22 mmol) and K₂CO₃ (0.442 g, 3.22 mmol) in 25 ml of ethanol was stirred and refluxed for 3 days. The mixture was poured into 25 ml of H₂O and extracted with CH₂Cl₂ (3 x 50 ml). The combined organic layers were washed with brine (25 ml) and dried (Na₂SO₄). Filtration and evaporation of the solvent gave a crude orange solid, which was purified by column chromatography (SiO₂ CH₂Cl₂/methanol (10:1)). Yield 42%. [α]²⁰D -11.7° (c 1.0, CH₂Cl₂). ¹H NMR δ 0.77 (s, 6H), 0.95 (s, 6H), 0.99-1.04 (m, 2H), 1.05 (s, 6H), 1.35-1.50 (m, 2H), 1.63-1.79 (m, 2H), 2.00 (d, J = 4.6 Hz, 2H), 2.27 (s, 6H), 2.44 (d, J = 7.0 Hz, 2H), 2.8-3.2 (broad signal,2H), 3.15 (bs, 1H), 3.21 (bs, 1H), 3.45 (d, J = 7.0 Hz, 2H), 3.7-4.0 (broad signal, 2H), 5.62-5.68 (m, 2H). ¹³C NMR δ 11.43 (q), 20.98 (q), 22.02 (q), 27.87 (t), 32.15 (t), 46.49 (s), 46.72 (d) 49.13 (s), 72.50 (d), 78.69 (d), 130.05 (d). N-alkyl signals were not observed in ¹³C NMR due to unknown reasons. HRMS calcd for C₂₇H₄₆N₂O₂: 418.356, found 418.356.

(+)-Cis-exo-3-(1-piperidinyl)isoborneol (4.4)

A mixture ofcis-exo-3-aminoisoborneol (4.1a) (4.95 g, 29.2 mmol), glutaric dialdehyde (25 wt% in H₂O) (5.9 g, 14.6 mmol), NaOAc (4.8 g, 58.5 mmol) and NaBH₃CN (3.7 g,
58.5 mmol) in 100 ml of ethanol was stirred at ambient temperature for 9 days. Excess of aqueous HCl (3M) was added carefully to destroy excess NaBH₄CN. The aqueous layer was adjusted to pH 10 with saturated aqueous Na₂CO₃ and extracted with CH₂Cl₂ (2 x 125 ml) and ethyl acetate (1 x 100 ml). The combined organic layers were washed with brine (100 ml) and dried (Na₂SO₄). Filtration and evaporation of the solvent gave a crude orange oil, which was purified by column chromatography (SiO₂, CH₂Cl₂/methanol (20:1)). Yield 1.73 g (50% compared to glutaric dialdehyde). All spectroscopic data were in good agreement with the given structure of 4.4 and similar as those described in Chapter 3.

(+)-1,3-Bis[5-methyl-1,2-cis-exo-bornane-3,5-oxazolidine-4-yl]propane (4.5)
A mixture of (+)-MAIB) (4.1b) (0.642 g, 3.5 mmol), glutaric dialdehyde (25 wt% in H₂O) (0.726 g, 1.8 mmol), NaOAc (0.590 g, 7.2 mmol) and NaBH₄CN (0.452 g, 7.2 mmol) in 25 ml of ethanol was stirred at ambient temperature for 2 days. Excess of aqueous HCl (3M) was added carefully to destroy excess NaBH₄CN. The aqueous layer was adjusted to pH 10 with saturated aqueous Na₂CO₃ and extracted with CH₂Cl₂ (3 x 50 ml) and ethyl acetate (1 x 50 ml). The combined organic layers were washed with brine (100 ml) and dried (Na₂SO₄). Filtration and evaporation of the solvent gave a 2:1 mixture of product and (+)-MAIB (according to H NMR). Column chromatography (SiO₂, CH₂Cl₂/methanol (20:1)) afforded compound 4.5 as a white solid in 60% yield. [α]₀²⁰ +30.7° (c 1.0, CHCl₃).¹ H NMR δ 0.79 (s, 6H), 0.81-0.88 (m, 2H), 0.96 (s, 6H), 1.18 (s, 6H), 1.35-1.74 (m, 14H), 2.26 (s, 6H), 2.35 (d, J = 7.7 Hz, 2H), 3.54-3.62 (m, 2H), 3.68 (d, J = 7.7 Hz, 2H).¹³C NMR δ 10.95 (q), 20.26 (q), 22.09 (t), 22.79 (q), 25.36 (t), 32.40 (t), 32.78 (t), 38.61 (q), 46.49 (s), 46.93 (d) 47.35 (s), 74.83 (d), 87.78 (d), 97.48 (d). HRMS calcd for C₂₇H₄₆N₂O₂: 430.356, found 430.356.

(+)-Cis-endo-N-monomethyl-3-aminoborneol ((+)-MAB) (4.8)
This compound was synthesised according to a literature procedure⁷ (see also text). However, in our hands the synthesis (under inert atmosphere) and purification of compound 4.7 was not that successful, yield ca. 50% (literature 85%).⁷ Reduction of 4.7 with LiAlH₄ in THF gave 4.8 in 96% yield.¹³H NMR and¹³C NMR data were in good agreement with the data found in the literature.⁷

(-)-N,N'-Bis[3-cis-endo-borneol]-N,N'-dimethyl-1,n-alkane (4.9)
General procedure for the synthesis of compounds 4.9a and 4.9b. A mixture of cis-endo-N-monomethyl-3-aminoborneol ((+)-MAB) (4.8) (1.00 g, 5.46 mmol), 1,₉-dibromoalkane (2.78 mmol) and K₂CO₃ (0.75 g, 5.46 mmol) in 50 ml of acetonitrile was stirred and refluxed for 16 h. The mixture was poured into 100 ml of H₂O and extracted
with diethyl ether (3 x 50 ml). The combined organic layers were washed with brine (50 ml) and dried (Na₂SO₄). Filtration and evaporation of the solvent gave crude 4.9, which was purified by column chromatography (SiO₂, CH₂Cl₂/methanol (10:1)) resulting in colourless oils which solidified upon standing. The physical data for compounds 4.9a and 4.9b are as follows:

(-)-N,N'-Bis[3-cis-endo-borneol]-N,N'-dimethyl-1,2-ethane (4.9a)
Yield 69%. ¹H NMR δ 0.84 (s, 6H), 0.87 (s, 12H), 1.08-1.22 (m, 2H), 1.35-1.75 (m, 4H), 1.87-2.12 (m, 4H), 1.9-2.4 (broad signal 4H), 2.17 (s, 6H), 2.74-2.81 (m, 2H), 2.93-2.98 (m, 2H), 3.79 (dd, J = 8.9 Hz, J = 1.3 Hz, 2H). ¹³C NMR δ 13.75 (q), 18.32 (q), 18.57 (t), 19.59 (q), 25.65 (t), 41.40 (q), 48.18 (s), 48.56 (d), 50.24 (s), 55.00 (t), 65.02 (d), 74.00 (d). HRMS calcd for C₂₄H₄₄N₂O₂: 392.340 found 392.340.

(-)-N,N'-Bis[3-cis-endo-borneol]-N,N'-dimethyl-1,3-propane (4.9b)
Yield 85%. [α]D²⁰ +53.8° (c 0.4, CH₂Cl₂). ¹H NMR δ 0.86 (s, 6H), 0.90 (s, 12H), 1.12-1.29 (m, 2H), 1.45-1.58 (m, 4H), 1.70-1.76 (m, 2H), 1.79-1.95 (m, 4H), 2.2-2.3 (bs, 2 x 3H, 2H), 2.45-2.55 (broad signal, 2H) 2.57 (dd, J = 8.7 Hz, J = 4.0 Hz, 2H), 3.66 (d, J = 8.7 Hz, 2H). ¹³C NMR δ 14.50 (q), 18.88 (q), 18.95 (t) 20.06 (q), 25.13 (t), 26.44 (t), 40.62 (q) 45.29 (s), 48.20 (d) 50.20 (s), 54.65 (t), 65.31 (d), 73.94 (d). HRMS calcd for C₂₅H₄₆N₂O₂: 406.356, found 406.356.

(+)-cis-endo-N-[[(1-methylpyrrol-2-yl)methyl]-N-methyl-3-aminoborneol (4.11)
Secondary amino alcohol 4.10 (0.80 g, 3.07 mmol), MeI (1.5 ml, excess), NaOH (4.0 g, excess) and 1 ml of H₂O were successively added to 25 ml of diethyl ether. The mixture was stirred for 16 h and an additional 1 ml of MeI was added. After another 24 h the mixture was poured into 50 ml of H₂O. The two layers were separated and the water phase was extracted with diethyl ether (3 x 30 ml). The combined organic layers were washed with brine (50 ml) and dried (Na₂SO₄). Filtration and evaporation of the solvent gave 0.73 g of a crude yellow solid. This material was recrystallised from 15 ml of hexane / ethyl acetate (10:1) yielding pure 4.11 as a white solid (0.70 g, 2.55 mmol, 83%); mp 54.9-56.4°C. [α]D²⁰ +61.4° (c 2.01, CH₂Cl₂). ¹H NMR δ 0.91 (s, 3H), 0.92 (s, 3H), 0.93 (s, 3H), 1.16-1.29 (m, 1H), 1.49-1.59 (m, 2H), 1.78-1.94 (m, 2H), 2.09 (s, 3H), 2.64 (dd, J = 8.6 Hz, J = 3.3 Hz, 1H), 3.33 (d, J = 13.6 Hz, AB system, 1H), 3.56 (d, J = 13.6 Hz, AB system, 1H), 3.66 (s, 3H), 3.75 (d, J = 8.6 Hz, 1H), 6.05 (m, 2H), 6.59 (m, 1H). ¹³C NMR δ 14.23 (q), 18.73 (q), 18.98 (t) 19.82 (q), 26.18 (t), 34.11 (q), 40.79 (q), 45.25 (s), 48.12 (d) 50.12 (s), 52.45 (t), 65.48 (d), 73.86 (d), 106.39 (d), 109.94 (d), 122.47 (d), 128.93 (s). HRMS calcd for C₁₇H₂₈N₂O₆: 276.220, found 276.220.

(+)-cis-endo-N-[2-pyridylmethyl]-N-methyl-3-aminoborneol (4.12)
Secondary amino alcohol 4.8 (1.00 g, 5.50 mmol), picolyl chloride hydrochloride (0.90
g, 5.50 mmol) and K$_2$CO$_3$ (1.66 g, 12.0 mmol) in 50 ml of acetonitrile was stirred and refluxed for 4 days. The reaction mixture was poured into 50 ml of H$_2$O and extracted with diethyl ether (2 x 50 ml). The combined organic layers were washed with brine (50 ml) and dried (Na$_2$SO$_4$). Filtration and evaporation of the solvent gave 0.73 g of a crude yellow oil. Column chromatography (SiO$_2$, CH$_2$Cl$_2$/methanol (5:1)) afforded compound 4.12 as a light yellow oil, which solidified upon standing. Yield 73%; mp 90.2-91.5°C. 

$[\alpha]_D^{\text{0}^\circ} +66.1^\circ$ (c 2.24, CH$_2$Cl$_2$). H NMR $\delta$ 0.88 (s, 3H), 0.89 (s, 3H), 0.92 (s, 3H), 1.12-1.29 (m, 1H), 1.48-1.63 (m, 2H), 1.78 (t, $J$ = 4.0, 1H) 1.82-1.96 (m, 1H), 2.12 (s, 3H), 2.82 (dd, $J$ = 8.8 Hz, $J$ = 4.0 Hz, 1H), 3.43 (d, $J$ = 13.8 Hz, AB system, 1H), 3.74 (d, $J$ = 8.8 Hz, 1H), 3.76 (d, $J$ = 13.8 Hz, AB system, 1H), 7.11-7.17 (m, 1H), 7.39 (d, $J$ = 7.8 Hz, 1H), 7.62 (dt, $J$ = 7.8 Hz, $J$ = 1.9 Hz, 1H), 8.53 (m, 1H) $^{13}$C NMR $\delta$ 14.23 (q), 18.65 (t) 19.81 (q), 26.18 (t), 41.15 (q), 45.05 (s), 48.11 (d) 50.22 (s), 62.69 (t), 64.54 (d), 73.93 (d), 121.89 (d), 122.40 (d), 136.36 (d), 149.07 (d) 159.10 (s). HRMS calcd for C$_{17}$H$_{26}$N$_2$O: 274.205, found 274.204.

Conjugate addition of diethylzinc to chalcone (4.13) or cyclohexenone (4.17) using catalytic amounts of Ni(acac)$_2$ and chiral amino alcohols

This procedure is typical for all conjugate addition reactions described in Section 4.3. A solution of Ni(acac)$_2$ (0.07 mmol) and chiral ligand (amounts, see Tables 4.1 and 4.2) in 2 ml of acetonitrile was stirred and refluxed for 1 h under nitrogen. In general this results in a clear green solution. Substrate was added (1.0-2.0 mmol), the mixture was cooled to -30°C and diethylzinc in hexane (1 M) or toluene (1.1 M) (1.5 equivalent) was added. Stirring was continued at -25°C for 16 h. An aliquot of the solution (0.1 ml) was taken and quenched with 1 ml of aqueous 1 N HCl. After extraction with 1 ml of diethyl ether the conversion was determined by GC analysis. Retention times (oven temperature 225°C, flow 101 ml/min He): 1,3-diphenyl-2-propenone (4.13), 5.66 min; 1,3-diphenylpentan-1-one (4.14), 4.93 min; (oven temperature 100°C, flow 101 ml/min He): cyclo-2-hexen-1-one (4.17), 2.87 min; 3-ethylcyclohexan-1-one (4.18), 5.88 min. If complete conversion was achieved, the mixture was poured into 25 ml of aqueous 1 N HCl and extracted with diethyl ether (3 x 20 ml). The combined organic layers were washed with brine (25 ml), dried (MgSO$_4$), filtered and evaporated to give the crude 1,4-products. (Caution: compound 4.18 is volatile and long evaporation times should be avoided.) After purification by column chromatography (SiO$_2$, hexane:diethyl ether 5:1) the e.e.’s were determined. 1,3-Diphenylpentan-1-one (4.14): HPLC analysis (see Section 3.8); 3-ethylcyclohexan-1-one (4.18): derivatisation with optically pure 1,2-diphenylethylene diamine followed by $^{13}$C NMR analysis, see also Chapter 5. All $^1$H NMR and $^{13}$C NMR data of 4.14 and 4.18 were in good agreement with the data found in Chapter 3.
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4.6 References and notes
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