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

Catalytic enantioselective annulations using 1,4-addition-aldol cyclization sequences

4.1 Introduction

There is a continued demand for novel routes to enantiomerically pure carbobicyclic compounds, a structural feature present in numerous natural products such as terpenes and steroids. A classical example of the use of enantiomerically pure carbobicyclic compounds is the synthesis of (±)-D-homo-19-nortestosterone starting from the readily available Wieland-Miescher ketone (4.1, n = 1). In the Hajos-Parrish asymmetric version of the Robinson annulation, using 3 mol% of l-proline for the intramolecular aldol condensation, the Wieland-Miescher ketone (4.1, n=1) is formed with 67% ee and can be obtained enantiomerically pure by crystallization (Scheme 4.1, I). This was one of the first enantioselective catalytic reactions of practical use in synthetic organic chemistry.

\[
\text{Scheme 4.1 The Hajos-Parrish asymmetric version of the Robinson annulation (I) vs the asymmetric 1,4-addition-aldol cyclization (II).}
\]

It can be envisioned that the use of an organozinc reagent bearing an appropriate functional group (i.e. an acetal) in the enantioselective 1,4-addition to 2-cycloalkenones, provides an alternative strategy for the synthesis of optically active bicyclic systems (Scheme 4.1, II). This approach towards annulation has already shown to be successful for non-enantioselective versions using functionalized Grignard reagents. Although the substitution pattern in the decalone products is different, both methods involve conjugate addition (a) and aldol cyclization (b) steps. The essential differences between the two methods are that: (i) the
cycloalkanone is the Michael donor in the first method and the acceptor in the new method, and (ii) the stereocontrol is exerted in the aldol step or in catalytic 1,4-addition step, respectively. Since it is already well established that functionalized organozinc reagents can be used in the copper-phosphoramidite catalyzed enantioselective 1,4-addition without loss of enantioselectivity, this approach could give such bicyclic products with high ee.

4.2 Enantioselective annulations via 1,4-addition-aldolcyclization of acetal functionalized organozinc reagents

4.2.1 Functionalized organozinc reagents

As was mentioned in Chapter 1, the two main advantages of organozinc reagents are their relatively low reactivity in combination with their ability to undergo transmetallations, which make organozinc reagents very useful for enantioselective catalysis. A further advantage, closely related to the aforementioned, is the fact that a lot of functional groups are tolerated in these organozinc reagents, e.g. esters, ketones, cyanides, halides, etcetera. Nowadays, a number of different methods for obtaining (functionalized) organozinc reagents is known, mainly due to the excellent work of Knochel and his coworkers. One of the most elegant procedure to prepare diorganozincs is the boron-zinc transmetalation method, starting from readily available alkenes, as first described by Knochel et al. in 1993 (Scheme 4.2).

\[
\begin{align*}
\text{FG-R} & \quad \text{HBEt}_2 \quad \text{FG-R} \quad \text{BEt}_2 \quad \text{Et}_2\text{Zn} \quad \text{FG-R} \quad \text{Zn} \\
\text{4.2} & \quad \text{4.3} & \quad \text{4.4} \\
\end{align*}
\]

Scheme 4.2 Preparation of diorganozincs using a boron-zinc exchange reaction as reported by Knochel et al.

Hydroboration of olefines 4.2 with Et\textsubscript{3}BH readily gives the trialkylboranes 4.3 with high regioselectivity. The organoboranes 4.3 readily react with diorganozinc reagents to give transmetalated products 4.4. Et\textsubscript{2}Zn is best suited for boron-zinc exchange reactions because of its high reactivity. By evaporation of the formed Et\textsubscript{3}B, the equilibrium of the transmetalation can be shifted to the right, to give zinc reagents 4.4 in high yield. This method is especially suitable for our purposes, the copper-phosphoramidite catalyzed enantioselective 1,4-addition of functionalized organozinc reagents, because it allows the easy preparation of “halide free” organozinc reagents. The use of “halide free” organozinc reagents is crucial, since the presence of halides in solution has a detrimental effect on the
enantioselectivity in the enantioselective 1,4-addition using copper-phosphoramidite catalysts.\textsuperscript{10}

### 4.2.2 Synthesis of acetal functionalized organozinc reagents

An organozinc reagent containing a protected aldehyde functionality is required to permit the ring closure to the desired bicyclic product after the enantioselective 1,4-addition (Scheme 4.1, II). Protection of the aldehyde is necessary to prevent reduction of the aldehyde in the hydroboration step. We therefore needed the acetals 4.7\textsuperscript{a-c} to construct 5, 6, and 7 membered rings respectively, using the intramolecular aldol condensation described in Scheme 4.2 (II). Acetal 4.7\textsuperscript{a} is commercially available and 4.7\textsuperscript{b} was prepared by the dimerization of ethyl vinyl ether (4.5) in the presence of Hg(OAc)\textsubscript{2}, according to a literature procedure.\textsuperscript{11} Acetal 4.7\textsuperscript{c} was prepared by reaction of commercially available 4.6 with triethyl orthoformate in the presence of Amberlyst\textsuperscript{®} 15 (Scheme 4.3).\textsuperscript{12} These mild conditions were chosen to prevent possible isomerization of the double bond.

![Scheme 4.3 Synthesis of acetals 4.7\textsuperscript{b-c}.](image)

The acetals 4.7\textsuperscript{a-c} were readily hydroborated in the presence of HBEt\textsubscript{2}, generated \textit{in situ} from 1 equivalent of BH\textsubscript{3} and 2 equivalents of Et\textsubscript{3}B, to give hydroborated products 4.8\textsuperscript{a-c}, as checked by \textsuperscript{1}H-NMR (Scheme 4.4).\textsuperscript{9b} The organoboranes 4.8\textsuperscript{b} and \textsuperscript{c} gave no problems in the transmetalation with neat Et\textsubscript{2}Zn at 0 °C, giving functionalized organozinc reagents 4.9\textsuperscript{b} and \textsuperscript{c} in 75% and 66% yield, respectively.

![Scheme 4.4 Preparation of acetal functionalized organozinc reagents 4.9\textsuperscript{a-c}.](image)
Transmetalation of 4.8a with Et₂Zn, however, did not give the desired organozinc reagent 4.9a, although a reaction had occurred according to 1H-NMR. The product formed rapidly evaporated upon stripping with toluene. The use of the compound obtained in this manner in the copper-phosphoramidite catalyzed 1,4-addition yielded almost exclusively the ethyl addition product. This information, together with the 1H-NMR data, which revealed the presence of an ethyl group connected to zinc in the reagent, led to the conclusion that mixed diorganozinc compound 4.10 was formed (Figure 4.1). Since the ethyl group is transferred to copper much easier than the acetal functionalized alkyl group, this explains the formation of 3-ethylcyclohexanone in the 1,4-addition. The reason for this incomplete transmetallation is not clear. A possible explanation is the coordination of an oxygen of the acetal group in 4.10 to the zinc, forming a 5-membered ring chelate, preventing transfer of the second acetal functionalized group (Figure 4.1).

4.10

Figure 4.1 Mixed diorganozinc reagent 4.10.

4.2.3 Acetal functionalized organozinc reagents in the catalytic enantioselective 1,4-addition

The organozinc reagents 4.9b and c were tested in the copper-phosphoramidite catalyzed enantioselective 1,4-addition to a series of cyclic enones (Scheme 4.5, Table 4.1). 3-(4,4-Diethoxybutyl)cyclohexanone (4.12a) was obtained in 91% yield and with an ee of 98% when 2-cyclohexenone 4.11a was treated with organozinc reagent 4.9b at −30 °C in the presence of the copper-phosphoramidite catalyst prepared in situ from 2 mol% Cu(OTf)₂ and 4 mol% (S,R,R)-L1. The enantioselectivity obtained with this functionalized organozinc reagent is comparable to that obtained with Et₂Zn. However, the reaction with 4.9b is much slower compared to the reaction with Et₂Zn under similar conditions. Whereas the reaction with Et₂Zn in the presence of 0.5 mol% Cu(OTf)₂ and 1 mol% (S,R,R)-L1 is complete within 1 h, the reaction with 4.9b is only complete after reaction overnight in the presence of 2 mol% Cu(OTf)₂ and 4 mol% (S,R,R)-L1. The use of 2 mol% of catalyst is necessary to perform the reaction, since the 1,4-addition of 4.9b to 2-cyclohexenone 4.11a in the presence 1 mol% Cu(OTf)₂ and 2 mol% (S,R,R)-L1 is not complete after reaction overnight (TLC).
Catalytic enantioselective annulations using 1,4-addition-aldol cyclization sequences

4.9b or 4.9c (2.0 equiv.)
Cu(OTf)$_2$ (2 mol%)
(S,R,R)-L1 (4 mol%)
toluene, −30 °C, 18 h

**Scheme 4.5** Catalytic enantioselective 1,4-addition of acetal functionalized organozinc reagents to 2-cycloalkenones 4.11a-e.

The addition reaction of 4.9b to 2-cycloheptenone (4.11b) and 2-cyclooctenone (4.11c) under the conditions as shown in Scheme 4.5 also proceeded smoothly, yielding the 1,4-addition products 4.12b and 4.12c, both in 61% yield (Table 4.1, entries 2 and 3). In the case of 4.12c, there was also a considerable amount of aldehyde present in the isolated product (~40%, $^1$H-NMR). The aldehyde was formed due to partial hydrolysis of the acetal on the column, since no aldehyde was present in the crude product before column chromatography.

**Table 4.1** Enantioselective 1,4-addition of organozinc reagents to 4.11a-e.

<table>
<thead>
<tr>
<th>entry</th>
<th>enone</th>
<th>organozinc reagent</th>
<th>product</th>
<th>c.y. (%)</th>
<th>e.e. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.11a</td>
<td>4.9b</td>
<td>4.12a</td>
<td>91</td>
<td>98</td>
</tr>
<tr>
<td>2</td>
<td>4.11b</td>
<td>4.9b</td>
<td>4.12b</td>
<td>61</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>4.11c</td>
<td>4.9b</td>
<td>4.12c</td>
<td>61$^a$</td>
<td>-</td>
</tr>
<tr>
<td>4$^d$</td>
<td>4.11d</td>
<td>4.9b</td>
<td>4.12d</td>
<td>49</td>
<td>98</td>
</tr>
<tr>
<td>5$^d$</td>
<td>4.11e</td>
<td>4.9b</td>
<td>4.12e</td>
<td>57$^b$</td>
<td>-</td>
</tr>
<tr>
<td>6</td>
<td>4.11a</td>
<td>4.9c</td>
<td>4.12f</td>
<td>43$^{a,b}$</td>
<td>-</td>
</tr>
</tbody>
</table>

(a) Isolated as a mixture of acetal and corresponding aldehyde due to partial hydrolysis during column chromatography. (b) Not optimized. (c) Not determined; see Table 4.2. (d) Reaction time 2 d.
Substituted 2-cyclohexenones 4.11d and 4.11e were also tested. In this case, the addition reaction was even more sluggish than with the unsubstituted 2-cycloalkenones; after 48 h some starting material was still present (TLC). This is probably due to increased steric hindrance between the bulky organozinc reagent and the substrates. Longer reaction times did not result in higher conversions. The very sluggish reaction may lead to poisoning of the catalyst at some stage, especially with the relatively “impure” functionalized organozinc reagents, preventing the reaction to reach completion. Consequently, the isolated yields of the products 4.12d and 4.12e were also lower, 49% and 57%, respectively. The ee of 4.12d was determined to be 98%, again demonstrating that the enantioselectivity is not negatively influenced by the change in organozinc reagent (vide supra).

Organozinc reagent 4.9c was used successfully also in the catalytic enantioselective 1,4-addition to 2-cyclohexenone (4.11a). In a preliminary experiment, after stirring overnight at −30 °C, the reaction product 4.12f was isolated in 43% yield as a mixture of acetal (60%) and corresponding aldehyde (40%) (vide supra, see also entry 3, Table 4.1).

4.2.4 Ring closure by acid catalyzed aldol condensation

Acid catalyzed ring closure of acetals 4.12a-e was performed with 1 M aqueous HCl in refluxing in THF, yielding the bicyclic structures 4.13a, b, d, e with isolated yields comparable to those reported in the literature for similar reactions (Scheme 4.6, Table 4.2).

Ee’s of the bicyclic products were determined by chiral GC and were 96% or higher in all cases except for 4.13e, which was only 84% (Table 4.2). The lower ee is not surprising since the addition of Et2Zn to 5,5-dimethyl-2-cyclohexenone (4.11e) also proceeds with somewhat lower ee (88%, see Chapter 3). The high ee found for 4.13d was especially rewarding since this compound has been used in a racemic form as the starting material for the synthesis of a precursor for an insect antifeedant. Attempts to perform the acid catalyzed cyclization on the crude acetal 4.12a did not give satisfactory results. This was probably due to the presence of 1,1-diethoxybutane, formed by protonation of 4.9b under aqueous basic conditions, giving rise to mixed aldol reactions.
Table 4.2 Acid catalyzed ring closures.

<table>
<thead>
<tr>
<th>entry</th>
<th>acetal</th>
<th>product</th>
<th>ring system</th>
<th>c.y. (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4.12a</td>
<td>4.13a</td>
<td>[6,6]</td>
<td>62</td>
<td>97</td>
</tr>
<tr>
<td>2</td>
<td>4.12b</td>
<td>4.13b</td>
<td>[7,6]</td>
<td>50</td>
<td>96</td>
</tr>
<tr>
<td>3</td>
<td>4.12c</td>
<td>4.13c</td>
<td>[8,6]</td>
<td>42&lt;sup&gt;a&lt;/sup&gt;</td>
<td>&gt;98</td>
</tr>
<tr>
<td>5</td>
<td>4.12e</td>
<td>4.13e</td>
<td>[6,6]</td>
<td>56</td>
<td>84</td>
</tr>
<tr>
<td>6</td>
<td>4.12f</td>
<td>4.13f</td>
<td>[6,7]</td>
<td>b</td>
<td>-</td>
</tr>
</tbody>
</table>

(a) Isolated yield over 2 steps (vide infra). (b) No ring closure.

Treating the mixture of acetal 4.12c and the corresponding aldehyde with aqueous HCl in THF at reflux overnight did not yield the dehydrated intramolecular aldol product 4.13c. Instead, an off-white solid was obtained, which was identified as ketol 4.14 (mixture of diastereomers) by <sup>1</sup>H-NMR and mass spectrometry (Scheme 4.7). Non-dehydrated aldol products were also observed in initial experiments with 4.12b and e upon workup after a few hours reaction time, but in these cases (nearly) complete conversion to the dehydrated product was observed after reaction overnight. When 4.14 was treated with aqueous HCl in THF under reflux for an additional 24 h, no dehydration was observed. Other methods to eliminate water from 4.14 also failed: silica in chloroform at RT, SOCl<sub>2</sub> in pyridine at 0 °C and KOH in methanol at RT<sup>16</sup>. Elimination of water was finally achieved by refluxing 4.14 in p-xylene with a catalytic amount of p-toluenesulfonic acid, to give 4.13c in 42% yield based on 4.12c.

![Scheme 4.7](image)

Scheme 4.7 Ring closure and dehydration to give 4.13c.

Treatment of 4.12f with aqueous HCl under the conditions of Scheme 4.6 to form a 7-membered ring did not lead to an intramolecular aldol condensation. In this case hydrolysis of 4.12f to the aldehyde was observed and no ring closed products were formed (<sup>1</sup>H-NMR)<sup>17</sup>. Attempts to perform the intramolecular aldol reaction with the aldehyde under basic conditions with 2,2,6,6-tetramethylpiperidine in refluxing chloroform only led to the isolation of starting material<sup>18</sup>. Treatment of the aldehyde of 4.12f with NaOEt in ethanol at RT gave a complicated mixture of products.<sup>19</sup> Since it is well established that ring closing reactions to rings larger than 6-membered is often difficult, or even impossible, because of the large negative entropy of activation,<sup>20</sup> no further attempts to form the 7-membered ring were performed.
4.3 Enantioselective annulations of 5-membered rings

The formation of carboheterocyclic structures incorporating a both a 5- and a 6-membered ring, i.e. a bicyclo[4.3.0]nonenone skeleton, represents an important extension to this asymmetric annulation methodology, since this bicyclic skeleton is found in many natural products.  

Because annulation of 5-membered rings through the introduction of organozinc reagent 4.9a was not feasible (Section 4.2.2) and addition of organozinc reagent 4.9b to cyclopentenone would not give a high enough enantioselectivity to be useful in a synthetic procedure (Scheme 4.8, I and II respectively), an alternative route had to be developed.

\[
\begin{align*}
\text{I} \quad & \quad \text{organozinc reagent not accessible} \\
\text{II} \quad & \quad \text{low enantioselectivity low yield}
\end{align*}
\]

**Scheme 4.8** Two possible approaches towards \([6,5]\) bicyclic systems and their disadvantages.

4.3.1 Catalytic enantioselective tandem 1,4-addition-allylic substitution

We anticipated that annulation of a 5-membered ring to a cycloalkenone might be achieved if the in situ prepared zinc enolate, resulting from the 1,4-addition, is prone to palladium catalyzed allylic substitution. The resulting disubstituted cycloalkanones can subsequently be functionalized further to give the desired bicyclic structures.

\[
\begin{align*}
\text{O} & \quad \text{Et}_2\text{Zn (1.2 equiv.)} \\
& \quad \text{Cu(OTf)}_2 (0.5 \text{ mol\%}) \\
& \quad (S,R,R)-\text{L1 (1.0 mol\%)} \\
& \quad \text{toluene, } -30 ^\circ \text{C} \\
\text{OZnEt} & \quad \text{Pd(PPh}_3)_4 (4 \text{ mol\%}) \\
& \quad 0 ^\circ \text{C, overnight}
\end{align*}
\]

**Scheme 4.9** Catalytic enantioselective tandem 1,4-addition-allylic substitution.

Such a regio-, diastereo-, and enantioselective three component coupling was indeed achieved when the enolate 4.15a, formed from reaction of 4.11a and Et₂Zn in the presence of
0.5 mol% of Cu(OTf)₂ and 1.0 mol% of (S,R,R)-L₁, was trapped with allyl acetate and a catalytic amount of Pd(PPh₃)₄ at 0 °C to give 4.16a (Scheme 4.9). A racemic version of this tandem addition, using an achiral sulfonamide ligand, was already published by Noyori et al.²⁴ in 1996. When the conversion to the zinc enolate 4.15a was completed, allyl acetate and Pd(PPh₃)₄ were added and the reaction mixture was allowed to warm to 0 °C, resulting in a clean reaction to 4.16a. This disubstituted cyclohexanone was isolated in 88% yield with an ee of 96% and an excellent trans/cis ratio of 9/1. The same diastereomeric ratio was reported by Noyori et al. for their racemic version of the same reaction and they determined that the major diastereomer of 4.16a had the trans configuration, as expected.²⁴a The tandem procedure shown in Scheme 4.9 is a nice example of two combined catalytic procedures where the product (4.15a) formed in the first catalytic cycle (for a detailed description; see Chapter 2) is directly used in the second, as is illustrated in Scheme 4.10.

Scheme 4.10  The product of catalytic cycle I is used in catalytic cycle II to yield 4.16a.

The tandem reaction shown in Scheme 4.9 has also been performed on a relatively large scale (5.0 g of 4.11a) with 2 mol% of Pd(PPh₃)₄, giving similar yields and selectivities. When the tandem addition was carried out by mixing all the components together at the beginning of the reaction at 0 °C, 4.16a was formed, but only in ~15% yield after 4 h (GC). Both the 1,4-addition and the allylic substitution proceeded much slower in this case compared to the successive addition. The 1,4-addition was almost completely inhibited after 3 h, leaving ~25% of 4.11a unreacted. This in contrast to the results found by Noyori et al., who report isolation of the product in comparable yields by this procedure. The difference in results can probably be explained by the different ligand systems used. The phosphorus containing ligands in our system also have a strong affinity for palladium, in contrast to the
sulfonamide ligands used by Noyori. Coordination of \((S,R,R)-L1\) to palladium would inhibit the 1,4-addition, explaining the slow and incomplete reaction.

The enantioselective tandem 1,4-addition-allylic substitution was also successful for 2-cycloheptenone (4.11b). In this case only the trans tandem addition product 4.16b was formed which was isolated in 86\% yield. More examples of this catalytic asymmetric tandem 1,4-addition-allylic substitution reaction will be described in Chapter 6.25

We anticipated that carrying out the tandem 1,4-addition-allylic substitution reaction in an intramolecular fashion by using organozinc reagent 4.17, containing an allyl acetate functionality, would give an elegant ring closing procedure. The 1,4-addition of 4.17 to 2-cyclohexenone would lead to zinc enolate 4.18, which upon treatment with Pd(PPh3)4 should give an intramolecular allylic substitution creating bicyclic system 4.19, containing 3 stereocentres, in a one-pot synthesis (Scheme 4.11).

\[
\begin{align*}
\text{HO} & \quad \text{Zn} & \quad \text{EtZn} & \quad \text{Pd(PPh\textsubscript{3})\textsubscript{4}} \\
\text{4.11a} & \quad \text{4.17} & \quad \text{4.18} & \quad \text{4.19}
\end{align*}
\]

Scheme 4.11 Potential one pot enantioselective ring closure by intramolecular allylic substitution.

However, we were unable to prepare the organozinc reagent 4.17 since hydroboration of diene 4.20 failed (Scheme 4.12). Treatment of diene 4.20 (prepared in three steps according to a literature procedure\textsuperscript{26}) with HBE\textsubscript{t} in THF at 0 °C, rather remarkably did not give any hydroboration product (1H-NMR). Warming to room temperature or 40 °C did not result in hydroboration either. Further attempts to prepare organozinc reagent 4.17 were not undertaken.

\[
\begin{align*}
\text{CH}_2\text{Cl}_2, 0 \degree \text{C,1 h} & \quad \text{4.20} \\
\text{AcCl, pyridine} & \quad \text{no reaction}
\end{align*}
\]

Scheme 4.12 Attempted synthesis of organozinc reagent 4.17 through hydroboration of 4.20.
4.3.2  **Wacker oxidation and base catalyzed aldol cyclization**

To perform the annulation of a 5-membered ring, the allyl side chains in 4.16a-b need to be converted into the methyl ketones. An excellent method to carry out this transformation in a single step is the so-called Wacker process.27 The Wacker process is used industrially to prepare acetaldehyde from ethylene,28 but is also suited for laboratory preparations.29 In the Wacker oxidation, PdCl₂ is used to oxidize an alkene according to the mechanism in Scheme 4.13. Since PdCl₂ is rather expensive, it is used in a catalytic amount and the formed Pd⁰ is oxidized back to Pd²⁺ by Cu²⁺, the co-oxidant. The Cu⁺ formed is reoxidized to Cu²⁺ by molecular oxygen.30

\[ \text{Scheme 4.13 Wacker oxidation.} \]

Treatment of 4.16a with 10 mol% of PdCl₂ and 1 equivalent of CuCl in a mixture of dimethylformamide (DMF) and water in an oxygen atmosphere led to a smooth conversion to methyl ketone 4.21a,31,32 which was isolated in 65% yield (Scheme 4.14).

\[ \text{Scheme 4.14 Annulation of 5-membered rings through a Wacker oxidation-aldol sequence.} \]

Ee determination by chiral GC showed that no racemization had taken place under these mild conditions. A welcome surprise was that the trans/cis ratio was improved during the Wacker oxidation of 4.16a. Starting with a 9/1 mixture of trans- and cis-4.16a a 35/1 mixture of trans- and cis-4.21a is obtained. Following the reaction by GC revealed that trans-4.16a
converted much faster to trans-4.21a than the cis-isomer converted to cis-4.21a. Thus, after reaction overnight most of the cis-4.16a still had not reacted, resulting in the observed diastereomeric enrichment. The terminal carbon-carbon double bond in 4.16b was readily converted to the methyl ketone also, allowing the isolation of trans-4.21b in 78% yield with 97% ee as a single diastereomer.

The first attempts to achieve ring closure of 4.21a to 4.22a with KOH in refluxing ethanol or water were not very successful.33 Although the desired product 4.22a was formed under these conditions, considerable amounts of two side products were also observed by 1H-NMR and GC. These side products turned out to be the isomers 4.23 and 4.24, formed by a shift of the double bond by deprotonation-protonation steps (Scheme 4.15). Analogous isomerizations have been reported previously for similar systems.34

![Scheme 4.15 Isomerization of 4.22a.](image)

To prevent the isomerization of 4.22a the cyclization was performed under slightly different conditions, using KOt-Bu and an aprotic solvent (THF) at ambient temperature. The sterically more hindered base was chosen also to prevent possible epimerization of the starting material 4.21a. Under these conditions the reaction proceeded smoothly and the isomerization reaction was sufficiently suppressed to isolate 4.22a in a reasonable yield with 96% ee and a trans/cis ratio of 13/1 (Scheme 4.14). Because the isomerization was not completely suppressed, it is essential to stop the reaction after 1 hour. Following the reaction by GC clearly showed that the isomerization reaction still occurs after prolonged reaction times and refluxing the reaction mixture after complete conversion to 4.21a for 2 hours led to the same mixture of 4.22a (60%), 4.23 (9%) and 4.24 (31%, GC) as in the initial attempts (using KOH in ethanol, vide supra). The base catalyzed aldol ring closure of 4.21b under comparable conditions led to the formation of 4.22b which was isolated in 82% yield with 96% ee. In this case only trans-4.22b was observed by GC and NMR, indicating that no epimerization had taken place.

### 4.4 Conclusions

The use of the functionalized organozinc reagent 4.9b in the catalytic enantioselective 1,4-addition to 2-cycloalkenones using Cu(OTf)₂ and (S,R,R)-L₁ leads to the same high enantioselectivities as the use of simple dialkylzinc reagents. The high enantioselectivity, together with the wide range of substrates tolerated by the catalyst, provides the basis for a
new asymmetric annulation method comprising two steps. In the first step the organozinc reagent 4.9b is added with high enantioselectivity to 2-cycloalkenones. The resulting acetals are hydrolyzed before undergoing subsequent intramolecular aldol reaction upon treatment with acid, to give (substituted) [6,6], [7,6] and [8,6] bicyclic systems with ee’s of 96% or higher. However, annulation of 5- or 7-membered rings by this method was not possible. In the first case the preparation of diorganozinc reagent 4.9a failed and in the second case the intramolecular aldol reaction did not proceed.

Annulation of 5-membered rings was achieved by a different strategy, using a catalytic enantioselective, regioselective, and diastereoselective three-component coupling. The in situ prepared zinc enolates 4.15a-b were trapped in a palladium catalyzed allylation, which was followed by a palladium catalyzed Wacker oxidation and a base catalyzed aldol cyclization. As an example, bicyclic systems 4.22a and b with a [6,5]- and [7,5]-structure, respectively, were prepared by this method, both with 96% ee.

Acknowledgement: Leggy Arnold is gratefully acknowledged for performing the important initial experiments leading to the annulation methodology described in Section 4.2 and for instructions concerning the preparation and handling of organozinc reagents.

4.5 Experimental section

General remarks

For general information: see Chapter 3. All the procedures involved in the preparation of functionalized diorganozinc compounds were performed in flame dried Schlenk vessels under an argon atmosphere. NMR measurements on boranes and organozinc reagents were performed in flame dried NMR tubes under an argon atmosphere. 1-Pentenal (4.6) was purchased from Lancaster and used as received. Compounds 4.7b and 4.20 were prepared according to literature procedures.

5,5-Diethoxy-1-pentene (4.7c)

1-Pentenal 4.6 (5.0 g, 59.4 mmol) was dissolved in triethyl orthoformate (40 ml, 5 equiv.) and 1.0 g Amberlyst® 15 was added (Caution!: 4.6 is an extremely foul smelling compound!). The mixture was stirred overnight at room temperature after which the Amberlyst® 15 was removed by filtration. Excess triethyl orthoformate and 4.7c were separated by fractional distillation through a long vigreux. Acetal 4.7c (5.3 g, 33.5 mmol, 56 %) was collected at 70-73 °C/40 mmHg as a colorles oil. 1H-NMR (CDCl₃, 300 MHz): δ 1.09 (t, J = 7.0 Hz, 6H), 1.6 (m, 2H), 2.0 (m, 2H), 3.3-3.6 (m, 4H), 4.38 (t, J = 5.9 Hz, 1H), 4.8-5.0 (m, 2H), 5.6-5.8 (m, 1H). 13C-NMR (CDCl₃, 300MHz): δ 15.29 (q), 28.94 (t), 32.66 (t), 60.96 (t), 102.31 (d), 114.64 (t), 138.03 (d).
General procedure for the preparation of diorganozinc reagents: Di-(4,4-diethoxybutyl)zinc (4.9b)

4,4-Diethoxy-1-butene 4.7b (5.0 g, 34.7 mmol) was cooled with liquid nitrogen, degassed under vacuum, and subsequently cooled with ice/water. In a second Schlenk vessel HBET₂ (34.7 mmol) was prepared by adding BEt₃ (23.1 ml, 1M solution in THF, 23.1 mmol) to BH₃·SMe₂ (5.8 ml, 2M solution in THF, 11.6 mmol) at 0 °C. The HBET₂ solution was transferred to the Schlenk vessel containing 4.7b via a cannula and the reaction mixture was slowly stirred for 1 h at 0 °C. The conversion was followed by taking aliquots of the reaction mixture, evaporating the volatiles and recording a ¹H-NMR spectrum (NMR data for trialkylborane 4.8b: ¹H-NMR (CDCl₃, 300 MHz): δ 0.6-0.9 (m, 4H), 1.0-1.2 (m, 14H), 1.3-1.4 (m, 2H), 1.4-1.5 (m, 2H), 3.3-3.6 (m, 4H), 4.3-4.4 (m, 1H). After complete conversion the volatiles were removed under vacuum (0.05 mmHg, 0 °C). The crude organoborane was treated with pure Et₂Zn (3.6 ml, 35.1 mmol) and the resulting dark grey reaction mixture was stirred for 3 h at 0 °C (Caution!: pure Et₂Zn is extremely pyrophoric!). Excess of Et₂Zn and the BEt₃ formed were removed under vacuum at 0 °C and the resulting gray oil was stripped with toluene (3 × 15 ml). The crude 4.9b was diluted with toluene (10 ml) and filtered over Celite®. Evaporation of the toluene yielded 4.9b (4.6 g, 13.0 mmol, 75%) as a yellow oil. ¹H-NMR (CDCl₃, 300 MHz): δ 0.17 (t, 4H), 1.16 (t, 6H), 1.5-1.6 (m, 8H), 3.4-3.6 (m, 8H), 4.53 (t, 2H). ¹³C-NMR (CDCl₃, 300 MHz): δ 13.22 (t), 15.21 (q), 21.52 (t), 37.78 (t), 61.47 (d), 103.81 (d). NMR data for Et₂Zn: ¹H-NMR (CDCl₃): δ 7.3 Hz, 4H), 1.18 (t, J = 7.1 Hz, 12H), 1.2-1.7 (m, 8H), 3.4-3.7 (m, 8H), 4.47 (t, J = 5.6 Hz, 2H). ¹³C-NMR (CDCl₃, 300 MHz): δ 15.22 (q), 15.48 (t), 26.03 (t), 31.11 (t), 33.11 (t), 60.59 (t), 103.02 (d).

Di-(5,5-diethoxypentyl)zinc (4.9c)

Starting from 4.7c (5.0 g, 31.6 mmol) the general procedure as outlined above was used to obtain 4.9c (4.0 g, 10.5 mmol, 66%) as a yellow oil. ¹H-NMR (CDCl₃, 300 MHz): δ 0.32 (t, J = 7.3 Hz, 4H), 1.18 (t, J = 7.1 Hz, 12H), 1.2-1.7 (m, 8H), 3.4-3.7 (m, 8H), 4.47 (t, J = 5.6 Hz, 2H). ¹³C-NMR (CDCl₃, 300 MHz): δ 15.22 (q), 15.48 (t), 26.03 (t), 31.11 (t), 33.11 (t), 60.59 (t), 103.02 (d).

General procedure for the catalytic enantioselective 1,4-addition of acetal functionalized organozinc reagents to 2-cycloalkenones: 3-(4,4-diethoxybutyl)cyclohexanone (4.12a)

Cu(OTf)₂ (8.7 mg, 0.024 mmol) and (S,R,R)-L₁ (26 mg, 0.048 mmol) were dissolved in toluene (20 ml) and stirred for 1 h at room temperature. The solution was cooled to −30 °C and 2-cyclohexenone (200 µl, 2.1 mmol) was added. After stirring for 10 min, organozinc reagent 4.9b (2.0 ml, 2 M solution in toluene, 4.0 mmol) was slowly added and the reaction mixture was stirred at −30 °C for 16 h after which complete conversion was reached as determined by TLC. The reaction was quenched with saturated aqueous NH₄Cl (25 ml) which had been brought to pH = 9 with ammonia beforehand. The organic layer was separated and the aqueous layer was extracted with ether (3 × 25 ml). The combined organic layers were washed with brine and dried over Na₂SO₄. Filtration and removal of the solvent was followed by column chromatography (SiO₂, hexanes:ether, 3:1) to give 4.12a as a colorless oil.
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(462 mg, 1.9 mmol, 91%). 1H-NMR (CDCl₃, 300 MHz): δ 1.18 (t, 6H), 1.3-1.4 (m, 6H), 1.5-2.0 (m, 6H), 2.3-2.4 (m, 3H), 3.45-3.65 (m, 4H), 4.45 (t, 1H). 13C-NMR (CDCl₃, 300 MHz): δ 15.31 (q), 21.85 (t), 25.21 (t), 31.22 (t), 33.71 (t), 36.38 (t). The ee of 4.12a was determined to be 98% by 13C-NMR taken of aminal 4.25 using the method of Alexakis et al.13:

![NMR data for 4.25](image)

Compounds 4.12 b-f were prepared according to the general procedure given for 4.12a (vide supra) with longer reactions times in the case of 4.12d and e (see Section 4.2.3). All reaction were performed on approximately 2 mmol scale, yields are given in Table 4.1:

3-(4,4-Diethoxybutyl)cycloheptanone (4.12b)

1H-NMR (CDCl₃, 300 MHz): δ 1.08 (t, J = 7.3 Hz, 6H), 1.1-1.9 (m, 13H), 2.2-2.4 (m, 4H), 3.4 (m, 4H), 4.35 (m, 1H). 13C-NMR (CDCl₃, 300 MHz): δ 15.31 (q), 22.05 (t), 24.36 (t), 28.47 (t), 33.61 (t), 35.94 (d), 36.69 (t), 37.03 (t), 43.84 (t), 49.84 (t), 60.90 (t), 60.96 (t), 102.72 (d), 214.48 (s). MS(CI) for C₁₅H₂₈O₃: m/z = 274 (M + NH₄)⁺.

3-(4,4-Diethoxybutyl)cyclooctanone (4.12c)

Compound 4.12c was isolated as a mixture with the corresponding aldehyde, see paragraph 4.2.3. Characteristic signals in 1H-NMR for 4.12c: 1H-NMR (CDCl₃, 300 MHz): δ 3.3-3.6 (m, 4H, 2× OCH₂), 4.36 (t, J = 5.8 Hz, 1H, -CH(OEt)₂). Characteristic signal for the corresponding aldehyde: δ 9.66 (s, 1H, -C(O)H).

3-(4,4-Diethoxybutyl)-4,4-dimethylcyclohexanone (4.12d)

1H-NMR (CDCl₃, 300 MHz): δ 0.87 (s, 3H), 0.90 (s, 3H), 1.09 (t, J = 7.0 Hz, 6H), 1.3-2.4 (m, 13H), 3.3-3.6 (m, 4H), 4.34 (m, 1H). 13C-NMR (CDCl₃, 300 MHz): δ 15.31 (q), 21.85 (d), 32.13 (q), 33.67 (t), 34.54 (q), 35.22 (s), 37.05 (t), 45.24 (t), 47.36 (t), 54.54 (t), 60.98 (t), 61.03 (t), 102.74 (d), 211.94 (s). MS(CI) for C₁₆H₃₀O₃: m/z = 288 (M + NH₄)⁺. The ee of 4.12d was determined to be 98% by 13C-NMR using the general method of Alexakis et al.13.

5-(4,4-Diethoxybutyl)-3,3-dimethylcyclohexanone (4.12e)

1H-NMR (CDCl₃, 300 MHz): δ 0.75 (s, 3H), 0.94 (s, 3H), 1.09 (m, 6H), 1.2-2.3 (m, 13H), 3.3-3.6 (m, 4H), 4.35 (m, 1H). 13C-NMR (CDCl₃, 300 MHz): δ 15.29 (q), 21.83 (t), 25.75 (d), 32.11 (q),
33.64 (t), 34.52 (q), 35.20 (s), 37.03 (t), 45.22 (t), 47.34 (t), 54.52 (t), 60.96 (t), 61.01 (t), 102.72 (d),
211.92 (s). MS(CI) for C_{16}H_{30}O_{3}: m/z = 288 (M + NH_{4})^+.

3-(5,5-Diethoxypentyl)cyclohexanone (4.12f)

Compound 4.12f was isolated as a mixture with the corresponding aldehyde, see paragraph 4.2.3. Characteristic signals in 1H-NMR for 4.12f: 1H-NMR (CDCl₃ / DMSO-d₆) δ 3.3-3.6 (m, 4H, 2 × OCH₂), 4.35 (t, J = 5.8 Hz, 1H, -CH(OEt)₂). Characteristic signal for the corresponding aldehyde: δ 9.63 (s, 1H, -C(O)H).

General procedure for the acid catalyzed ring closure: 3,4,4a,5,6,7-hexahydro-1(2H)-naphthalenone (4.13a)

Acetal 4.13a (250 mg, 1.03 mmol) was dissolved in a mixture of THF (3 ml) and 1 M aqueous HCl (2.5 ml) and the reaction mixture was refluxed overnight. After quenching with 5% aqueous NaHCO₃ (5 ml), ether (10 ml) was added and the aqueous layer was extracted with ether (2 × 10 ml) and the combined organic layers were washed with water (5 ml) and brine (5 ml), respectively, and dried over Na₂SO₄. Filtration and removal of the solvent was followed by column chromatography (SiO₂, hexanes:ether, 3:1) yielded 4.13a as a colorless oil (95 mg, 0.63 mmol, 61%). 1H-NMR (CDCl₃ / DMSO-d₆) δ 1.3-1.6 (m, 2H), 1.96-2.3 (m, 3H), 3.1 (s, 3H), 3.8-4.2 (m, 4H), 6.92 (m, 1H). 13C-NMR (CDCl₃, 300 MHz): δ 21.33 (t), 22.46 (t), 26.10 (t), 30.26 (t), 31.50 (t), 37.73 (t), 40.26 (d), 135.92 (s), 140.00 (d), 201.35 (s). HRMS calcd for C₁₀H₁₄O: 150.104; Found: 150.105. An ee of 97% was determined by chiral GC on a Chiraldex G-TA column.

Compounds 4.13b,d,e were prepared according to the general procedure given for 4.13a (vide supra). Yields are given in Table 4.2:

1,2,3,6,7,8,9,9a-Octahydro-5H-benzo[a]cyclohepten-5-one (4.13b)

1H-NMR (CDCl₃, 300 MHz): δ 0.8-1.0 (m, 1H), 1.2-2.0 (m, 8H), 2.15 (m, 2H), 2.4-2.7 (m, 4H), 6.92 (m, 1H). 13C-NMR (CDCl₃, 300 MHz): δ 20.48 (t), 26.08 (t), 26.91 (t), 27.50 (t), 30.55 (t), 32.68 (t), 36.01 (d), 39.31 (t), 138.10 (d), 203.01 (s). An ee of 96% was determined by chiral GC on a Chiraldex G-TA column, 150 °C isothermic, t_{ret} 24.0 min (major enantiomer), t_{ret} 26.0 min (minor enantiomer).

4,4-Dimethyl-3,4a,5,6,7-hexahydro-1(2H)-naphthalenone (4.13d)

1H-NMR (CDCl₃, 300 MHz): δ 0.77 (s, 3H), 0.94 (s, 3H), 1.0-2.4 (m, 11H), 6.8 (m, 1H). 13C-NMR (CDCl₃, 300 MHz): δ 19.41 (q), 21.52 (t), 23.68 (t), 26.13 (t), 28.85 (q), 32.52 (s), 35.90 (t), 37.80 (t), 46.39 (d), 137.68 (s), 138.52 (d), 200.54 (s). An ee of >98% was determined by chiral GC on a Chiraldex G-TA column, 150 °C isothermic, t_{ret} 26.6 min (major enantiomer), t_{ret} 27.5 min (minor enantiomer).

3,3-Dimethyl-3,4a,5,6,7-hexahydro-1(2H)-naphthalenone (4.13e)

1H-NMR (CDCl₃, 300 MHz): δ 0.97 (s, 3H), 1.01 (s, 3H), 1.1-2.6 (m, 11H), 6.64 (m, 1H). 13C-NMR (CDCl₃, 300 MHz): δ 21.61 (t), 26.12 (q), 26.17 (t), 30.35 (t), 31.82 (s), 31.87 (q), 33.37 (d),
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44.75 (t), 53.81 (t), 135.33 (d), 139.04 (s), 201.91 (s). An ee of 84% was determined by chiral GC on a Chiraldex G-TA column, 150 °C isothermic, $t_{ret}$ 20.5 min (major enantiomer), $t_{ret}$ 22.2 min (minor enantiomer).

2,3,6,7,8,9,10,10a-Octahydrobenzo[a]cycloocten-5(1H)-one (4.13c)

Treatment of acetal 4.12c under the conditions outlined in the general procedure yielded hydroxyketone 4.14 as an off-white solid as the crude product. $^1$H-NMR (CDCl$_3$): δ 0.8-2.4 (br, 19H), 3.7-3.8 (m, 1H, -HC(OH)-). MS(EI) for C$_{12}$H$_{20}$O$_2$: m/z = 196 (M$^+$. Hydroxyketone 4.14 (180 mg, 0.92 mmol) and p-toluenesulfonic acid (~ 10 mg) were dissolved in p-xylene (5 ml) and refluxed overnight. The reaction mixture was quenched with 5% aqueous NaHCO$_3$ (5 ml) and ethyl acetate was added (10 ml). The aqueous layer was extracted with ethyl acetate (2 × 10 ml) and the combined organic layers were washed with water (5 ml) en brine (5 ml), respectively, and dried over Na$_2$SO$_4$. Filtration and evaporation of the solvent was followed by column chromatography (SiO$_2$, hexanes:ethyl acetate, 3:1) to give 4.13c as a colorless oil (101 mg, 0.57 mmol, 62%, 42% overall). $^1$H-NMR (CDCl$_3$, 300 MHz): δ 0.8-1.0 (m, 1H), 1.2-1.8 (m, 11H), 2.1 (m, 2H), 2.1-2.2 (m, 1H), 2.6-2.8 (m, 2H), 6.60 (t, $J$ = 4.0 Hz, 1H). $^{13}$C-NMR (CDCl$_3$, 300 MHz): δ 17.38 (t), 25.32 (t), 25.86 (t), 26.88 (t), 29.98 (t), 31.04 (d), 36.60 (t), 39.43 (t), 136.62 (d), 142.10 (s), 207.27 (s). HRMS calcd for C$_{12}$H$_{18}$O: 178.136; Found: 178.135. An ee of >98% was determined by chiral GC on a Chiraldex G-TA column, 145 °C isothermic, $t_{ret}$ 42.9 min (major enantiomer), $t_{ret}$ 44.5 min (minor enantiomer).

$(2R, 3S)$-2-Allyl-3-ethylcyclohexanone (4.16a)

Cu(OTf)$_2$ (22.7 mg, 0.063 mmol) and (S,R,R)-L1 (67.3 mg, 0.125 mmol) were dissolved in toluene (30 ml) and stirred for 1 h at RT. The solution was cooled to −30 °C and 2-cyclohexenone (0.50 ml, 5.2 mmol) was added. The solution was stirred for 10 min after which Et$_2$Zn (5.2 ml, 1.1M in toluene, 5.7 mmol) was added slowly. After stirring for 3 h at −30 °C, Pd(PPh$_3$)$_4$ (120 mg, 0.1 mmol) and allyl acetate (0.56 ml, 5.2 mmol) were added and the reaction mixture was allowed to warm up to 0 °C and stirred overnight. The reaction mixture was quenched with aqueous 2N HCl (30 ml) and the layers were separated. The aqueous layer was extracted with ether (4 × 25 ml) and the combined organic layers were washed with brine and dried over MgSO$_4$. After filtration and removal of the solvent crude 4.16a was purified by column chromatography (SiO$_2$, hexanes:ether, 3:1) after which 761 mg (4.6 mmol, 88%) of 4.16a was isolated as a colorless oil. $^1$H-NMR (CDCl$_3$, 300 MHz): 0.78 (t, 3H), 1.1-2.4 (m, 12H), 4.88 (m, 2H), 5.67 (m, 1H). $^{13}$C-NMR (CDCl$_3$, 300 MHz): 10.41 (q), 24.90 (t), 25.72 (t), 28.36 (t), 31.40 (t), 41.80 (t), 43.18 (d), 54.61 (d), 115.91 (t), 136.45 (d), 212.92 (s). An ee of 96% was determined by chiral GC on a Chiraldex G-TA column, 145 °C isothermic, $t_{ret}$ 23.8 min ((2S, 3R)-4.16a, trans/ minor), $t_{ret}$ 24.7 min ((2R, 3S)-4.16a, trans/ major).

trans-2-Allyl-3-ethylcycloheptanone (4.16b)

Disubstituted cycloheptanone 4.16b was prepared starting from 4.11b according to the procedure outlined for 4.16a in 86% yield. $^1$H-NMR (CDCl$_3$, 300 MHz): δ 0.88 (t, $J$ = 7.3 Hz,
(2R, 3S)-3-Ethyl-2-(2-oxopropyl)cyclohexanone (4.21a)

CuCl (416 mg, 4.2 mmol) and PdCl$_2$ (74 mg, 0.42 mmol) were suspended in DMF (14 ml) and water (2 ml). The suspension was brought under an oxygen atmosphere and was stirred for 1 h after which it turned green. Allylic compound 4.16a (695 mg, 4.2 mmol) was added dropwise and the mixture was stirred overnight at RT under oxygen atmosphere. The reaction was quenched with 30 ml 2N HCl (aq) and the aqueous layer was extracted with ether (3 × 25 ml). The combined organic layers were washed with 5% NaHCO$_3$ (25 ml) and brine (25 ml) and dried over Na$_2$SO$_4$. Filtration and removal of solvents gave crude 4.21a which was purified by column chromatography (SiO$_2$, hexanes:ether, 4:1) yielding 497 mg (2.7 mmol, 65%) of pure 4.21a. $^1$H-NMR (CDCl$_3$, 300MHz): 0.79 (t, 3H), 1.0-2.0 (m, 7H), 2.11 (s, 3H), 2.24 (m, 3H), 2.70 (m, 2H). $^{13}$C-NMR (CDCl$_3$, 300MHz): 10.20 (q), 25.85 (t), 26.46 (t), 29.91 (t), 30.43 (q), 40.17 (t), 44.59 (d), 51.25 (d), 207.91 (s), 211.63 (s). An ee of 96% was determined by chiral GC on a Chiraldex G-TA column, 140 °C isothermic, $t_{\text{ret}}$ 32.1 min ((2R, 3S)-4.21a, trans/major), $t_{\text{ret}}$ 34.1 min ((2R, 3S)-4.21a, trans/minor).

trans-3-Ethyl-2-(2-oxopropyl)cycloheptanone (4.21b)

Diketone 4.21b was prepared starting from 4.16b according to the procedure outlined for 4.21a in 78% yield. $^1$H-NMR (CDCl$_3$, 300 MHz): $\delta$ 0.86 (t, J = 7.3 Hz, 3H), 1.2-1.9 (m, 9H), 2.12 (s, 3H), 2.3-2.7 (m, 3H), 3.0 (m, 2H). $^{13}$C-NMR (CDCl$_3$, 300MHz): $\delta$ 11.15 (q), 23.15 (t), 24.12 (t), 26.12 (t), 29.94 (q), 30.57 (t), 40.15 (d), 42.99 (t), 44.67 (t), 49.91 (d), 51.25 (d), 207.91 (s), 211.63 (s). An ee of 96% was determined by chiral GC on a Chiraldex G-TA column, 160 °C isothermic, $t_{\text{ret}}$ 23.7 min (major enantiomer), $t_{\text{ret}}$ 24.2 min (minor enantiomer).

(7S,7aR)-7-Ethyl-1,4,5,6,7,7a-hexahydro-2H-inden-2-one (4.22a)

Under argon in flame dried glassware 123 mg (1.10 mmol) KOtBu was dissolved in 10 ml of THF. Compound 4.22a (200 mg, 1.10 mmol) was added dropwise and the reaction mixture was stirred at RT for 1 h after which it was quenched with 15 ml of NH$_4$Cl (aq). The layers were separated and the aqueous layer was extracted with ether (3 × 20 ml). The combined organic layers were washed with brine and dried over Na$_2$SO$_4$. After filtration and evaporation crude 4.22a was obtained. Purification by column chromatography (SiO$_2$, hexanes:ether, 3:2) yielded 101 mg (0.62 mmol, 56%) of 4.22a as a slightly yellow oil with an e.e. of 96%. $^1$H-NMR (CDCl$_3$, 300Hz): 0.88 (t, 3H), 1.0-2.8 (m, 12H). $^{13}$C-NMR (CDCl$_3$, 300MHz): 10.96 (q), 26.46 (t), 27.71 (t), 29.94 (t), 30.08 (t), 41.09 (t), 47.02 (d), 126.72 (d), 184.58 (s), 208.96 (s). HRMS calcd for C$_{11}$H$_{16}$O: 164.120; Found: 164.125. An ee of 96% was determination by chiral GC on a CP-Cyclodextrine-β-2,3,6-M-1g column, 125 °C isothermic, $t_{\text{ret}}$ 126.2 min ((7S,7aR)-4.22a, trans/major), $t_{\text{ret}}$ 137.4 min ((7R,7aS)-4.22a, trans/minor), $t_{\text{ret}}$ 134.5 min ((7S,7aS)-4.22a, cis/major), $t_{\text{ret}}$ 142.5 min ((7R,7aR)-4.22a, cis/minor).
**trans-4-Ethyl-3a,4,5,6,7,8-hexahydro-2(3H)-azulenone (4.22b)**

Bicyclic compound 4.22b was prepared starting from 4.21b according to the procedure outlined above for 4.22a in 82% yield. 1H-NMR (CDCl₃): δ 0.87 (t, J = 7.3 Hz, 3H), 1.1-2.2 (m, 10H), 2.4-2.8 (m, 4H), 5.83 (s, 1H). 13C-NMR (CDCl₃): δ 25.88 (t), 28.35 (t), 30.80 (t), 31.40 (t), 43.50 (d), 45.14 (d), 49.43 (t), 103.02 (d), 186.58 (s), 208.76 (s). HRMS calcd for C₁₂H₁₈O: 178.136; Found: 178.137. An ee of 96% was determined by chiral GC on a CP-Cyclodextrin-β-2,3,6-M-1g column.

### 4.6 References and notes


10 The 1,4-addition of EtZnCl in the presence of \((S,R,R)-L1\) under standard conditions gives racemic products: L. A. Arnold, undergraduate research report, Groningen, 1997. The presence of halides and diorganozinc reagents could give rise to a Schlenk equilibrium, producing RZnX species, thus explaining the detrimental effect of halides on the enantioselectivity.


13 The ee was determined by \(^{13}\text{C}-\text{NMR}\) after derivatization with \((1R,2R)-1,2\)-diphenylethlenediamine; A. Alexakis, J. C. Frutos, P. Mangeney, \textit{Tetrahedron: Asymmetry} \textbf{1993}, \textit{4}, 2431.

14 The organozinc reagents prepared by the boron-zinc transmetalation reaction are not really purified (see experimental section) and will therefore contain more impurities than commercialyl available simple organozinc reagents.


17 The ethylene glycol acetal of \textit{4.12f} can also be hydrolyzed to the aldehyde without concomitant ring closure: J. F. Gil, D. J. Ramón, M. Yus, \textit{Tetrahedron} \textbf{1993}, \textit{49}, 4923.


23 It should be mentioned that in the mean time Hoveyda \textit{et al.} have reached an impresive ee of 97% for the 1,4-addition of EtZn to 2-cyclopentenone making method II feasible, see also Chapter 2; S. J. Degrado, H. Mizutani, A. H. Hoveyda, \textit{J. Am. Chem. Soc.} \textbf{2001}, \textit{123}, 755.


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31 The use of CuCl is preferred over the use of CuCl₂ since the latter can give rise to the formation of chlorinated ketones: J. Tsuji, I. Shimizu, K. Yamamoto, *Tetrahedron Lett.* 1976, 34, 2975.


