Asymmetric catalysis in the synthesis of cis-cyclopropyl containing fatty acids and the addition of Grignard reagents to carbonyl compounds
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Chapter 4

Copper(I)-catalyzed asymmetric alkylation of aldehydes with Grignard reagents: A direct access to secondary alcohols

In this chapter the asymmetric copper-catalyzed 1,2-addition of Grignard reagents to aryl aldehydes and \( \alpha,\beta \)-unsaturated aldehydes is described. Due to a higher reactivity of aldehydes compared to ketones, a lower enantioselectivity was observed, therefore different additives have been studied to enhance the enantioselectivity of the addition reaction.
4.1 Introduction

The asymmetric 1,2-addition of organometallic reagents to aldehydes is a fundamental reaction to form enantioenriched secondary alcohols. The great interest to synthesize enantioenriched secondary alcohols derives from occurrence of this moiety in many natural products, fragrances and biological active compounds. The first attempts to perform this alkylation with Grignard reagents in an asymmetric manner were carried out in the presence of stoichiometric amounts of chiral auxiliaries or chiral modifiers. In 1984, Oguni et al. reported the first catalytic enantioselective alkylation of benzaldehyde with diethylzinc as organometallic reagent and different amino alcohols as chiral catalyst (Scheme 4.1).

Scheme 4.1. First catalytic enantioselective addition of an organometallic reagent to benzaldehyde.

Further developments in the enantioselective addition of dialkylzinc reagents to aldehydes were reported by Noyori and co-workers. Their studies focused on the mechanism and showed that less reactive organometallic reagents than magnesium or lithium reagents were essential to reach high enantioselectivities in the alkylation of aldehydes (Scheme 4.2).

Scheme 4.2. Developments towards a catalytic system for the alkylation of aldehydes.

A drawback in the use of dialkylzinc reagents is the thermal instability of their higher homologs. One option to prepare diorganozinc reagents in situ is by transmetallation of Grignard reagents to zinc salts (ZnX₂, X: Cl, Br and OMe). This method was
Applied by Seebach et al. in the addition of dialkylzinc compounds to aldehydes in the presence of a spirotitanium complex as chiral catalyst (Scheme 4.3). In this one-pot procedure it is crucial to separate the precipitated magnesium salts before using the solution in the alkylation, otherwise a low enantioselectivity is observed due to the competing racemic reaction promoted by these salts. As a further optimization of this procedure, Seebach and co-workers reported in 1994 the direct use of Grignard reagents in the transmetallation to Ti(O-iPr)₃Cl forming the less reactive organotitanium reagent, which then was used in combination with Ti-TADDOLate as catalyst for the asymmetric 1,2-addition to aldehydes. A significant improvement was described by Harada et al. since in their catalytic system the magnesium salts from the transmetallation could remain in the R-Ti(O-iPr)₃ solution and still high enantioselectivities were reached (Scheme 4.4).
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Scheme 4.4. Optimized procedure for the asymmetric alkylation of aldehydes by Harada et al..

Additional studies by Da et al. showed that the amount of Ti(OiPr)₄ can be reduced to 0.9 eq by using a chelating additive bis[2-(N,N-dimethylamino)ethyl] ether (BDMAEE), that makes the removal of magnesium salts unnecessary.¹¹,¹² With this catalytic system a variety of Grignard reagents were tolerated and the scope of the aromatic aldehydes could be broadened (Scheme 4.5).

Scheme 4.5. Enantioselective alkylation of aldehydes with BDMAEE as chelating agent.

In the latest study of Yus et al. a new catalytic system based on Ti(OiPr)₄, an Ar-BINMOL ligand (L1) and various Grignard reagents, in particular MeMgBr, was reported. This catalytic system allows not only alkylation to aromatic aldehydes, also aliphatic aldehydes undergo the reaction with high yields and high enantioselectivities (Scheme 4.6).¹³,¹⁴
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Scheme 4.6. Latest development in the alkylation of aliphatic aldehydes with MeMgBr.

In the asymmetric alkylation with titanium organyls and catalytic amounts of ligands, high enantioselectivities are reached, because of well-defined intermediates in which the alkyl group can be transferred specifically to one face of the carbonyl double bond. Still a major drawback is the huge access of Ti(OiPr)₄ used in most of the protocols. Thus, we saw the need to develop a new catalytic system, in which only catalytic amounts of ligand and metal precursors are used. Recently we reported a new procedure for the asymmetric copper(I)-catalyzed 1,2-addition of Grignard reagents to α,β-unsaturated ketones.₁⁵,₁⁶ Those optimized conditions were applied in initial studies to α,β-unsaturated aldehydes (Scheme 4.7).₁⁷

Scheme 4.7. Application of the copper-catalyzed alkylation to α,β-unsaturated aldehydes.

4.2 Goal of this study

In this study we applied the optimized reaction conditions for the 1,2-addition of Grignard reagents to aryl ketones, in the corresponding reaction to aryl aldehydes and α,β-unsaturated aldehydes. In the preliminary studies (Scheme 4.7), an
enhancement of the ee was observed when 15 mol% iPrOH was used as an additive in the alkylation to \( \alpha,\beta \)-unsaturated aldehydes. We tried to understand this observation and tested, whether the same effect was observed for aryl aldehydes.

### 4.3 Results and discussion

In the first set of experiments (Table 4.1, entries 1 and 2), the conditions, as previously described, were used in the 1,2-addition to aldehyde 1. The observed yields and enantioselectivities are in the same range as previously described (Scheme 4.7).!

<table>
<thead>
<tr>
<th>entry</th>
<th>product</th>
<th>T</th>
<th>solvent</th>
<th>additive</th>
<th>ee(^a)</th>
<th>ratio (^b) 1:2</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
<td>(-78 ^\circ C)</td>
<td>MTBE</td>
<td>no</td>
<td>59%</td>
<td>9:91</td>
</tr>
<tr>
<td>2</td>
<td>2</td>
<td>(-78 ^\circ C)</td>
<td>MTBE</td>
<td>20 mol% iPrOH</td>
<td>81%</td>
<td>14:86</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>(-78 ^\circ C)</td>
<td>diisopropyl ether</td>
<td>no</td>
<td>55%</td>
<td>1:99</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>(-78 ^\circ C)</td>
<td>CH(_2)Cl(_2)</td>
<td>no</td>
<td>29%</td>
<td>4:96</td>
</tr>
<tr>
<td>5</td>
<td>2</td>
<td>(-83 ^\circ C)</td>
<td>MTBE</td>
<td>no</td>
<td>51%</td>
<td>6:94</td>
</tr>
</tbody>
</table>

\(^a\) The enantiomeric excess was determined by HPLC, Chiralcel OD-H column, n-heptane/i-PrOH 99:1, 40 \(^\circ C\) isotherm, detection at 254 nm, retention time (min): 17.9 (major) and 20.0 (minor). \(^b\) Ratio determined by GC-MS analysis. \(^c\) 1.8 eq Grignard reagent.

The influence of the solvent was studied, to increase the enantioselectivity (entries 3 and 4). The reaction in diisopropyl ether gave similar results and the reaction with dichloromethane as solvent gave only 29\% ee; therefore MTBE was used as solvent.
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for the further screening. It was tried to increase the ee by lowering the temperature to -83 °C (entry 5), but this had no significant influence. In all reactions in this study, generally around 5% of the starting material was not converted. This might be due to the formation of a stable copper(III)-complex, which then does not further transfer the alkyl group. The nature of the copper(III) intermediates are studied by rapid injection NMR in the group of Ogle et al.18

In the subsequent reactions, the optimized conditions were applied to aryl aldehyde 3. In this case, around 20% of 1,2-reduction product 5 was observed as side product (see ratio of starting material to products 4 and 5, Table 4.2). This side product is formed due to β-hydride transfer from the Grignard reagent. This problem occurs especially with branched Grignard reagents.

Table 4.2. Optimizing the reaction conditions with aryl aldehyde 3.

<table>
<thead>
<tr>
<th>entry</th>
<th>product</th>
<th>solvent</th>
<th>additive</th>
<th>ee</th>
<th>ratio [%] of 3:4:5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>4a</td>
<td>MTBE</td>
<td>no</td>
<td>33%</td>
<td>35:50:15</td>
</tr>
<tr>
<td>2</td>
<td>4a</td>
<td>MTBE</td>
<td>15 mol% iPrOH</td>
<td>34%</td>
<td>88:9:3</td>
</tr>
<tr>
<td>3</td>
<td>4a</td>
<td>MTBE</td>
<td>30 mol% iPrOH</td>
<td>37%</td>
<td>5:75:20</td>
</tr>
<tr>
<td>4</td>
<td>4a</td>
<td>MTBE</td>
<td>60 mol% iPrOH</td>
<td>37%</td>
<td>8:71:21</td>
</tr>
</tbody>
</table>
In the first set of reactions, 2-ethylbutylimagnesium bromide was used in the addition to aldehyde 3 (entries 1-4). The ee of alcohol 4a is 30% lower compared to alcohol 2, and in addition there was no enhancement of the ee observed when iPrOH was added to the reaction mixture. Even the amount of additive had no influence on the enantioselectivity. Especially, the reaction in entry 2 shows only 9% conversion. To exclude that the decrease in ee resulted from the Grignard reagent used, the reactions were repeated with isobutylmagnesium bromide to give the secondary alcohol 4b (entries 5 and 6). The ee in the standard reaction stays in the range of 30%, but in the reaction with iPrOH as additive only 12% ee was observed. Further attempts to increase the enantioselectivity, by breaking the magnesium aggregates using LiCl as an additive, failed. The inverse addition, that is, the addition of aldehyde 3 to the reaction mixture containing the full amount of Grignard reagent, gave only 32% ee. By changing the concentration of the reaction mixture to a more dilute solution a similar ee of 27% was observed.

\[\text{entry} \quad \text{product} \quad \text{solvent} \quad \text{additive} \quad \text{ee} \quad \text{ratio [%]}\]

<table>
<thead>
<tr>
<th>entry</th>
<th>product</th>
<th>solvent</th>
<th>additive</th>
<th>ee [%]</th>
<th>ratio [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>4b</td>
<td>MTBE</td>
<td>no</td>
<td>30%</td>
<td>7:77:16</td>
</tr>
<tr>
<td>6</td>
<td>4b</td>
<td>MTBE</td>
<td>20 mol% iPrOH[\text{*}]</td>
<td>12%</td>
<td>n.d.</td>
</tr>
<tr>
<td>7</td>
<td>4b</td>
<td>MTBE</td>
<td>10 mol% LiCl</td>
<td>27%</td>
<td>n.d.</td>
</tr>
<tr>
<td>8[\text{c}]</td>
<td>4b</td>
<td>MTBE</td>
<td>no</td>
<td>32%</td>
<td>4:79:17</td>
</tr>
<tr>
<td>9[\text{c}]</td>
<td>4b</td>
<td>MTBE</td>
<td>no</td>
<td>27%</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

\[\text{* The enantiomeric excess was determined by HPLC, Chiralpak AD-H column, n-heptane/i-PrOH 98:2, 40 °C isotherm, detection at 210 nm, retention time (min): 18.6 (major) and 21.1 (minor). Ratio determined by GC-MS analysis.} \]

2 eq Grignard reagent. \[\text{c} \]2.3 eq Grignard reagent. \[\text{d} \]1.8 eq Grignard reagent. \[\text{e} \]2.0 eq Grignard reagent. \[\text{f} \]Reverse addition, addition of aldehyde to the reaction mixture. \[\text{g} \]Diluted reaction mixture c = 0.018 M; standard concentration: c = 0.075 M.
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In the screening of various aryl aldehydes, aldehyde 6 gave the highest ee with 51%, therefore the reaction conditions were optimized using this substrate. First, diisopropyl ether and dichloromethane were used as solvents, but in both cases no increase in enantioselectivity was observed.

Table 4.3. Further investigations for optimal reaction conditions using aldehyde 6.

<table>
<thead>
<tr>
<th>entry</th>
<th>product</th>
<th>ligand</th>
<th>catalyst loading</th>
<th>additive</th>
<th>ee</th>
<th>ratio [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7</td>
<td>L2</td>
<td>6 mol%</td>
<td>no</td>
<td>51%</td>
<td>11:80:9</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>L2</td>
<td>6 mol%</td>
<td>DME 20 mol%</td>
<td>33%</td>
<td>10:76:14</td>
</tr>
<tr>
<td>3</td>
<td>7</td>
<td>L2</td>
<td>6 mol%</td>
<td>BDMAEE 20 mol%</td>
<td>43%</td>
<td>11:76:13</td>
</tr>
<tr>
<td>4</td>
<td>7</td>
<td>L2</td>
<td>20 mol%</td>
<td>no</td>
<td>76%</td>
<td>8:87:5</td>
</tr>
<tr>
<td>5</td>
<td>7</td>
<td>L2</td>
<td>6 mol%</td>
<td>no</td>
<td>51%</td>
<td>4:79:17</td>
</tr>
<tr>
<td>6</td>
<td>7</td>
<td>L3</td>
<td>6 mol%</td>
<td>no</td>
<td>19%</td>
<td>n.d.</td>
</tr>
<tr>
<td>7</td>
<td>7</td>
<td>L4</td>
<td>6 mol%</td>
<td>no</td>
<td>21%</td>
<td>n.d.</td>
</tr>
<tr>
<td>8</td>
<td>7</td>
<td>L5</td>
<td>6 mol%</td>
<td>no rac</td>
<td>n.d.</td>
<td>n.d.</td>
</tr>
</tbody>
</table>

a The enantiomeric excess was determined by HPLC, Chiralcel OJ-H column, n-heptane/i-PrOH 98:2, 40 °C isotherm, detection at 215 nm, retention time (min): 20.8 (minor) and 25.4 (major). b Ratio determined by GC-MS analysis. c Reverse addition, addition of aldehyde to the reaction mixture.
Furthermore, 1,2-dimethoxyethane (DME) and BDMAEE were used as additives to chelate free magnesium salts to prevent the racemic background reaction (Table 4.3, entries 2 and 3). This turned out to be not the case; enantioselectivities between 30 to 40% were reached. An increase of ee was observed only when 20 mol% of the catalyst was used (entry 4). As previously for aldehyde 3, also for aldehyde 6 a reverse addition gave no increase of enantioselectivity. Additionally, two other ferrocene ligands, L3 and L4, and one phosphoramidite ligand, L5, were investigated (entries 6-8). L2 gave the highest ee in this set of ligands. For this reason the further screening of the reaction was performed with L2 in MTBE at -78 °C.

In the subsequent set of experiments, different aryl aldehydes were applied, which either have a different structure or carry an electron-withdrawing or -donating substituent on the phenyl ring. In addition we tested also 2-thiophenecarboxaldehyde as an example of a heterocyclic compound (Table 4.4). In the case of the unsubstituted aromatic aldehyde 9a and the two naphthyl aldehydes 9b, 9c (Table 4.4, entries 1-3) one can see an increase in ee, with increasing bulk close to the carbonyl double bond. In contrast to this is the low ee of compound 10d (entry 4), where one face should be more shielded by the methyl group in ortho position. The highest ee is observed with substrate 9g (entry 7), the low yield of this product is due to the volatility of the compound.

Table 4.4. Screening different aryl aldehydes

<table>
<thead>
<tr>
<th>entry</th>
<th>Substrate</th>
<th>yield</th>
<th>ee</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>9a</td>
<td>10a 30%</td>
<td>27%</td>
</tr>
<tr>
<td>2</td>
<td>9b</td>
<td>10b 18%</td>
<td>45%</td>
</tr>
<tr>
<td>3</td>
<td>9c</td>
<td>10c 44%</td>
<td>52%</td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>entry</th>
<th>Substrate</th>
<th>yield&lt;sup&gt;a&lt;/sup&gt;</th>
<th>ee&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>4</td>
<td>9d</td>
<td>10d 40%</td>
<td>26%</td>
</tr>
<tr>
<td>5</td>
<td>9e</td>
<td>10e 48%</td>
<td>43%</td>
</tr>
<tr>
<td>6</td>
<td>9f</td>
<td>10f 30%</td>
<td>23%</td>
</tr>
<tr>
<td>7</td>
<td>9g</td>
<td>10g 6%</td>
<td>67%</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated yield after work-up and purification by column chromatography. <sup>b</sup> The enantiomeric excess was determined by HPLC, for details see experimental section.

The enantioselectivities of the secondary alcohols derived from aryl aldehydes are between 23-67% due to the fast blank reaction. For the blank reaction substrate 9d was used, and after 14 h 75% of conversion to alcohol 10d was observed. Thus, the focus was turned again to α,β-unsaturated aldehydes since in the initial studies high enantioselectivities were obtained with these substrates (Scheme 4.7). For an easier comparison with the aryl aldehydes, the matching α,β-unsaturated aldehydes 15g and 15h were synthesized in three steps (Scheme 4.8). In the first step aldehyde 9 was reacted with the commercially available HWE reagent 12 to give α,β-unsaturated ester 13. For both esters 13g and 13h only the E-double bond isomer was identified by NMR. The ester was reduced with DIBAlH to alcohol 14, which was subsequently selectively oxidized with a mixture of TPAP and NMO to α,β-unsaturated aldehyde 15.
Next, the synthesized α,β-unsaturated aldehydes were tested in the asymmetric 1,2-addition of Grignard reagents applying two different sets of conditions (Scheme 4.9). With condition 1, standard conditions are meant and in condition 2, 20 mol% iPrOH was used as an additive and the Grignard reagent was added slowly.

The results shown in Scheme 4.9 are preliminary results. The conversion was determined by GC-MS analysis, and the compounds were not further characterized by NMR or HRMS. The enantiomeric excess was determined by HPLC. For aldehyde 15h, in both cases a similar ee of 64% was reached, which means also for this substituted α,β-unsaturated aldehyde no enhancement of ee was observed when
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iPrOH was added to the reaction mixture. Surprisingly, substrate 15g gave even a lower ee than its matching aryl aldehyde.

4.4 Conclusion

We investigated the copper(I)-catalyzed 1,2-addition of Grignard reagents to aryl aldehydes. In comparison to the aryl ketones, for the aryl aldehydes lower enantioselectivities were observed (30-60% ee). The selectivity decreases due to the higher reactivity of aldehydes in comparison to ketones. In addition, the magnesium salts (MgBr₂) in the reaction mixture catalyze the blank reaction, this phenomenon was first described by Harada et al.¹⁰ Our attempts to chelate the free magnesium salts or to break the magnesium clusters with LiCl showed also no effect on the ee. No influence on the enantioselectivity was observed, when the aldehyde was added slowly to the reaction mixture. This supports the effect of a fast blank reaction, since in the reaction one drop of the aldehyde solution should be surrounded by more molecules of the chiral catalyst than in the addition the other way around.

The enhancement of ee when iPrOH was used, was only observed for aldehyde 1. The enantioselectivity seems to be independent of the amount of iPrOH used in the reaction, as we showed for aldehyde 3. The conversion of the substrates was never complete, there was always around 4-10% starting material left, this might be due to the formation of a stabilized copper(III) intermediate.¹⁸ In reactions of aryl aldehydes all the time there was 1,2-reduction product as by-product observed.

In summary the best set of conditions for the 1,2-addition of aldehydes with Grignard reagents is the copper-complex with L₂ in MTBE at -78 °C. Future studies should investigate the mechanism (Figure 4.1), to understand the coordination of copper to the carbonyl double bond. One option to study the activated complex or copper intermediates, would be rapid injection NMR. With this technique, Ogle et al. showed a difference in coordination depending on the copper source, and the coordination of copper to the double bond in a methyl vinyl ketone.¹⁸,¹⁹ Based on those investigations new ligands can be designed, to reach a higher differentiation of the two faces of the carbonyl double bond to increase the enantioselectivity. Another crucial point is the prevention of the activation of the carbonyl double bond by the free magnesium salts.

![Figure 4.1. Proposed transition state of the reaction.](image-url)
4.5 Experimental

For general information see experimental of chapter 2.

4.5.1 Alkylation of aryl aldehydes

General procedure for the copper-catalyzed 1,2-addition

CuBr·SMe$_2$ (0.015 mmol, 5 mol%) and (S,R)$_-$reverse Josiphos (L$_2$) (0.018 mmol, 6 mol%) were dissolved in dry MTBE (4 mL) and stirred at room temperature for 15 min. To this mixture was added the corresponding aldehyde (0.6 mmol, 1 eq) in 4 mL dry MTBE. Then the mixture was cooled to −78 °C. After stirring for 15 min at −78 °C, the corresponding Grignard reagent (0.72 mmol, 1.2 eq) was added over 30 min. The reaction mixture was stirred at −78 °C for 14 h. The reaction was quenched with 1 mL MeOH and 2 mL saturated aq. NH$_4$Cl. After the reaction mixture reached rt, the layers were separated and the water layer was extracted three times with CH$_2$Cl$_2$. The combined organic layers were dried over MgSO$_4$, filtered and the filtrate was concentrated in vacuo. From the crude product a sample was taken for GC-MS analysis to determine the ratio of the 1,2-addition product, reduction product and starting material. The enantiomeric ratio was determined after purification by column chromatography.

3-methyl-1-phenylbutan-1-ol (10a)$^{11}$

The title compound was prepared from aldehyde 9a following the general procedure. Purification by column chromatography (SiO$_2$, pentane/diethyl ether 9:1) afforded 10a as a light yellow oil (29.6 mg, 0.180 mmol, 30%, 27% ee). $^1$H NMR (400.0 MHz, CDCl$_3$): δ ppm 7.35-7.19 (m, 5H), 4.20-4.10 (m, 1H), 1.75-1.57 (m, 3H), 1.46-1.40 (m, 1H), 0.90 (dd, 6H). $^{13}$C NMR (100.6 MHz, CDCl$_3$): δ ppm 144.2 (C), 128.5 (3xCH), 125.8 (2xCH), 72.8 (CH), 48.3 (CH$_2$), 24.8 (CH), 23.1 (CH$_3$), 22.2 (CH$_3$). The enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel OD-H column, n-heptane/i-PrOH 95:5, 40 °C isotherm, detection at 215 nm, retention time (min): 12.8 (minor) and 13.2 (major).

3-methyl-1-(naphthalen-1-yl)butan-1-ol (10b)$^{11}$

The title compound was prepared from aldehyde 9b following the general procedure. Purification by column chromatography (SiO$_2$, pentane/diethyl ether 9:1) afforded 10b as yellow oil (23.4 mg, 0.109 mmol, 18%, 45% ee). $^1$H NMR (400.0 MHz,
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CDCl₃): δ ppm 7.85-7.82 (m, 3H), 7.79 (s, 1H), 7.51-7.49 (m, 3H), 4.93 (m, 1H), 1.88 (s, 1H), 1.86-1.79 (m, 2H), 1.78-1.71 (m, 1H), 0.99-0.97 (dd, 6H). ¹³C NMR (100.6 MHz, CDCl₃): δ ppm 142.5 (C), 133.3 (C), 132.9 (C), 128.3 (CH), 127.9 (CH), 127.7 (CH), 126.1 (CH), 125.8 (CH), 124.5 (CH), 124.1 (CH), 72.9 (CH), 48.2 (CH₂), 24.9 (CH), 23.1 (CH₃), 22.3 (CH₃). The enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel OJ-H column, n-heptane/i-PrOH 98:2, 40 °C isotherm, detection at 214 nm, retention time (min): 45.8 (minor) and 52.5 (major).

3-methyl-1-(naphthalen-1-yl)butan-1-ol (10c)¹¹

HO

The title compound was prepared from aldehyde 9c following the general procedure. Purification by column chromatography (SiO₂, pentane/diethyl ether 9:1) afforded 10c as a light yellow oil (56.3 mg, 0.263 mmol, 44%, 52% ee). ¹H NMR (400.0 MHz, CDCl₃): δ ppm 8.11 (d, 1H), 7.88 (d, 1H), 7.78 (d, 1H), 7.66 (d, 1H), 7.55-7.46 (m, 3H), 5.57 (d, 1H), 2.00-1.92 (m, 2H), 1.85 (m, 1H), 1.72 (m, 1H), 0.99-0.97 (dd, 6H). ¹³C NMR (100.6 MHz, CDCl₃): δ ppm 141.0 (C), 133.8 (C), 130.3 (C), 128.9 (CH), 127.8 (CH), 126.0 (CH), 125.5 (2xCH), 123.0 (CH), 122.0 (CH), 69.3 (CH), 47.7 (CH₂), 25.3 (CH), 23.6 (CH₃), 21.9 (CH₃). The enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel OJ-H column, n-heptane/i-PrOH 98:2, 40 °C isotherm, detection at 254 nm, retention time (min): 20.1 (minor) and 24.1 (major).

1-(2,5-dimethylphenyl)-3-methylbutan-1-ol (10d)

HO

The title compound was prepared from aldehyde 9d following the general procedure. Purification by column chromatography (SiO₂, pentane/diethyl ether 9:1) afforded 10d as light yellow oil (45.8 mg, 0.238 mmol, 40%, 26% ee). ¹H NMR (400.0 MHz, CDCl₃): δ ppm 7.30 (s, 1H), 7.00 (q, 2H), 4.99 (dd, 1H), 2.33 (s, 3H), 2.29 (s, 3H), 1.94-1.80 (m, 1H), 1.71-1.64 (m, 3H), 0.99 (dd, 6H). ¹³C NMR (100.6 MHz, CDCl₃): δ ppm 143.3 (C), 135.8 (C), 130.9 (C), 130.3 (CH), 127.7 (CH), 125.6 (CH), 68.8 (CH), 47.6 (CH₂), 25.0 (CH), 23.6 (CH₃), 21.1 (CH₃), 21.1 (CH₃), 18.5 (CH₃). HRMS was not measured. The enantiomeric ratio was determined by chiral HPLC analysis, Chiralpak AD-H column, n-heptane/i-PrOH 98:2, 40 °C isotherm, detection at 210 nm, retention time (min): 18.8 (major) and 21.3 (minor).
1-(4-fluorophenyl)-3-methylbutan-1-ol (10e)\textsuperscript{11}

\[
\begin{align*}
\text{F} & \quad \text{OH} \\
\text{CF}_3 & \quad \text{OH}
\end{align*}
\]

The title compound was prepared from aldehyde 9e following the general procedure. Purification by column chromatography (SiO\textsubscript{2}, pentane/diethyl ether 9:1) afforded 10e as yellow oil (53.2 mg, 0.292 mmol, 48%, 43% ee). \textsuperscript{1}H NMR (400.0 MHz, CDCl\textsubscript{3}): δ ppm 7.30 (dd, 2H), 7.02 (dd, 2H), 4.76-4.68 (m, 1H), 1.88 (br s, 1H), 1.76-1.61 (m, 2H), 1.53-1.40 (m, 1H), 0.94 (dd, 6H). \textsuperscript{13}C NMR (100.6 MHz, CDCl\textsubscript{3}): δ ppm 163.3 (C), 140.9 (C), 127.5 (CH), 127.4 (CH), 115.3 (CH), 115.1 (CH), 72.1 (CH), 48.4 (CH\textsubscript{2}), 24.7 (CH), 23.1 (CH\textsubscript{2}), 22.2 (CH\textsubscript{3}). The enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel AS-H column, n-heptane/i-PrOH 100:0, 40 °C isotherm, detection at 254 nm, retention time (min): 44.3 (major) and 49.9 (minor).

3-methyl-1-(3-(trifluoromethyl)phenyl)butan-1-ol (10f)

\[
\begin{align*}
\text{CF}_3 & \quad \text{OH} \\
\text{O} & \quad \text{OH}
\end{align*}
\]

The title compound was prepared from aldehyde 9f following the general procedure. Purification by column chromatography (SiO\textsubscript{2}, pentane/diethyl ether 9:1) afforded 10f as light yellow oil (42.9 mg, 0.185 mmol, 30%, 23% ee). \textsuperscript{1}H NMR (400.0 MHz, CDCl\textsubscript{3}): δ ppm 7.61 (s, 1H), 7.52 (d, 2H), 7.48-7.41 (m, 1H), 4.82-4.79 (m, 1H), 2.06 (br s, 1H), 1.77-1.69 (m, 2H), 1.51-1.45 (m, 1H), 0.96 (dd, 6H). \textsuperscript{13}C NMR (100.6 MHz, CDCl\textsubscript{3}): δ ppm 146.3 (C), 130.6 (C), 129.2 (CH), 128.8 (CH), 122.6 (2xCH), 72.1 (CH), 48.4 (CH\textsubscript{2}), 24.7 (CH), 23.2 (CH\textsubscript{2}), 22.7 (CH\textsubscript{3}). HRMS was not measured. The enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel OD-H column, n-heptane/i-PrOH 95:5, 40 °C isotherm, detection at 215 nm, retention time (min): 9.3 (minor) and 10.0 (major).

3-methyl-1-(thiophen-2-yl)butan-1-ol (10g)\textsuperscript{11}

\[
\begin{align*}
\text{S} & \quad \text{OH} \\
\text{O} & \quad \text{OH}
\end{align*}
\]

The title compound was prepared from aldehyde 9g following the general procedure. Purification by column chromatography (SiO\textsubscript{2}, pentane/diethyl ether 9:1) afforded 10g as light yellow oil (6.5 mg, 0.038 mmol, 6%, 67% ee). \textsuperscript{1}H NMR (400.0 MHz, CDCl\textsubscript{3}): δ ppm 7.25 (d, 1H), 6.98-6.95 (m, 1H), 5.03-4.99 (m, 1H), 1.89 (br s, 1H), 1.84-1.61 (m, 3H), 0.96 (dd, 6H). \textsuperscript{13}C NMR (100.6 MHz, CDCl\textsubscript{3}): δ ppm 143.3 (C), 130.6 (C), 127.7 (CH), 125.5 (CH), 68.8 (CH), 47.6 (CH\textsubscript{2}), 25.0 (CH), 23.6 (CH\textsubscript{2}), 21.7 (CH\textsubscript{3}). The enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel OD-H column, n-heptane/i-PrOH 95:5, 40 °C isotherm, detection at 233 nm, retention time (min): 12.7 (minor) and 13.6 (major).
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4.5.2 Synthesis of α,β-unsaturated aldehydes (15)

**General procedure for the synthesis of α,β-unsaturated ester (13)**

![Chemical structure](image)

HWE reagent 12 (1.6 eq) was dissolved in 18 mL dry THF and cooled with an ice bath. At this temperature n-BuLi (1.6 M hexane solution, 1.3 eq) was added to the reaction mixture and stirred for 30 min. Then aldehyde 9 (1.0 eq) was added as solution in 2 mL THF. The reaction mixture was stirred overnight, while warming to rt. The reaction was quenched by adding saturated aq. NH₄Cl solution. The layers were separated and the water layer was extracted three times with diethyl ether. The combined organic layers were dried over MgSO₄, filtered and the filtrate was concentrated in vacuo. The α,β-unsaturated ester 13 was isolated after purification by column chromatography.

**({E})-ethyl 2-methyl-3-(thiophen-2-yl)acrylate (13g)**

The title compound was prepared from aldehyde 9g (0.30 mL, 2.62 mmol) following the general procedure. Purification by column chromatography (SiO₂, pentane/diethyl ether 9:1) afforded 13g as yellow oil (300 mg, 1.53 mmol, 58%). ¹H NMR (400.0 MHz, CDCl₃): δ ppm 7.75 (s, 1H), 7.35 (d, 1H), 7.16 (d, 1H), 6.99 (dd, 1H), 4.16 (q, 2H), 2.11 (s, 3H), 1.24 (t, 3H). ¹³C NMR (100.6 MHz, CDCl₃): δ ppm 168.4 (C), 139.3 (C), 131.6 (CH), 131.4 (CH), 129.0 (CH), 127.3 (CH), 124.9 (C), 60.9 (CH₂), 14.3 (CH₃), 14.2 (CH₃). HRMS was not measured.

**({E})-ethyl 2-methyl-3-({m}-tolyl)acrylate (13h)**

The title compound was prepared from aldehyde 9h (0.47 mL, 4 mmol) following the general procedure. Purification by column chromatography (SiO₂, pentane/diethyl ether 9:1) afforded 13h as yellow oil (758 mg, 3.71 mmol, 93%). ¹H NMR (400.0 MHz, CDCl₃): δ ppm 7.61 (s, 1H), 7.52 (d, 2H), 7.48-7.41 (m, 1H), 4.20 (q, 2H), 2.06 (s, 6H), 1.24 (t, 3H). ¹³C NMR (100.6 MHz, CDCl₃): δ ppm 168.4 (C), 139.3 (C), 131.6 (CH), 131.4 (CH), 129.0 (CH), 127.3 (CH), 124.9 (C), 60.9 (CH₂), 14.3 (CH₃), 14.2 (CH₃). HRMS was not measured.
Chapter 4

General procedure for the synthesis of \( \alpha, \beta \)-unsaturated aldehyde (15)

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{DIBAlH, Et}_2\text{O} & \quad 78 \degree \text{C, 16 h} \\
\text{NMO, TPAP} & \quad \text{DCM, rt, 14 h}
\end{align*}
\]

Ester 13 (1 eq) was dissolved in 5 mL dry diethyl ether and cooled to -50 \(^\circ\)C. At this temperature DIBAlH (1 M THF solution, 2.2 eq) was added and the reaction mixture was stirred till all starting material was consumed (followed by TLC). The reaction was quenched by adding saturated aq. Rochelle’s salt solution (potassium sodium tartrate) and this mixture was stirred for 1 h, for easier separation. The layers were separated and the water layer was extracted three times with diethyl ether. The combined organic layers were dried over MgSO\(_4\), filtered and the filtrate was concentrated \textit{in vacuo}. The crude \( \alpha, \beta \)-unsaturated alcohol 14 was immediately used in the oxidation reaction to \( \alpha, \beta \)-unsaturated aldehyde 15.

Alcohol 14 (1 eq) was dissolved in dry DCM, and to this was added NMO (1.3 eq) and TPAP (5 mol%). The reaction mixture was stirred at rt for 14 h (reaction progress controlled by TLC). Most of the solvent was evaporated under reduced pressure and \( \alpha, \beta \)-unsaturated aldehyde 15 was isolated after purification by column chromatography.

\((E)-2\text{-methyl-3-(thiophen-2-yl)prop-2-en-1-ol (15g)}\)

The title compound was prepared from ester 13g (550 mg, 2.80 mmol) following the general procedure. Purification by column chromatography (SiO\(_2\), pentane/diethyl ether 3:1) afforded 15g as yellow oil (175 mg, 1.15 mmol, 41% over two steps). \(^1\)H NMR (400.0 MHz, CDCl\(_3\)): \( \delta \) ppm 9.52 (s, 1H), 7.60 (d, 1H), 7.42 (s, 1H), 7.39 (d, 1H) 7.17 (dd, 1H), 2.09 (s, 3H). \(^1\)C NMR (100.6 MHz, CDCl\(_3\)): \( \delta \) ppm 197.2 (CH), 144.8 (CH), 141.8 (C), 138.0 (C), 135.7 (CH), 134.1 (CH), 130.7 (CH), 13.7 (CH\(_3\)). HRMS was not measured.

\((E)-2\text{-methyl-3-(m-tolyl)prop-2-en-1-ol (15h)}\)

The title compound was prepared from ester 13h (300 mg, 1.47 mmol) following general procedure. Purification by column chromatography (SiO\(_2\), pentane/diethyl ether 9:1) afforded 15h as yellow oil (183 mg, 1.14 mmol, 77% over two steps). \(^1\)H NMR (400.0 MHz, CDCl\(_3\)): \( \delta \) ppm 9.58 (s, 1H), 7.35 (d, 1H), 7.34 (d, 2H), 7.24-7.20 (m, 2H), 2.06 (s, 3H). \(^1\)C NMR (100.6 MHz, CDCl\(_3\)): \( \delta \) ppm 195.6 (CH), 150.1 (CH), 138.4 (C), 138.2 (C), 135.1 (C), 130.7
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(\text{CH}), 130.4 (\text{CH}), 128.6 (\text{CH}), 127.1 (\text{CH}), 21.4 (\text{CH}_3), 11.0 (\text{CH}_3). HRMS was not measured.

**\text{(S,E)-2,5-dimethyl-1-(thiophen-2-yl)hex-1-en-3-ol (16g)}**

The enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel OD-H column, \text{n-heptane/i-PrOH} 99:1, 40 °C isotherm, detection at 274 nm, retention time (min): 39.2 (major) and 45.5 (minor).

**\text{(S,E)-2,5-dimethyl-1-(m-tolyl)hex-1-en-3-ol (16h)}**

The enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel OD-H column, \text{n-heptane/i-PrOH} 99:1, 40 °C isotherm, detection at 209 nm, retention time (min): 21.7 (major) and 24.8 (minor).

### 4.6 References


