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 5
Enantioselective copper(I)-catalyzed alkylation of aryl alkyl ketones with Grignard reagents

A further application of a new catalytic system, the combination of copper(I) and (S,Ro)-reverse Josiphos, in the 1,2-addition of Grignard reagents to aryl alkyl ketones is presented. A study of the influence of the substitution pattern of the phenyl ring on the enantioselectivity showed, that substitution at the meta position is preferred. The limit of the reaction in terms of reactivity was found, when biaryl ketones were used as starting material.

Parts of this chapter will be published:

5.1 Introduction

Tertiary alcohols are a general motif found in many natural products, pharmaceuticals and crop protection products. This functional group is challenging to synthesize. One way to form tertiary alcohols is the asymmetric 1,2-addition of organometallic reagents to ketones, so forming a new C-C bond. This stereoselective addition comes with two problems: first the low electrophilicity of the carbonyl group influences the reactivity, and second the steric similarity of substituents surrounding the carbonyl group makes the discrimination between the two faces of the double bond difficult. For these reasons, there are not much efficient catalyst systems reported promoting the addition with high enantioselectivities, as for the corresponding reaction with aldehydes (see for more details chapter 4). Therefore, the development of new catalytic systems creating such stereocenters in an asymmetric fashion, are of great importance.

Fu and co-workers were the first to report this reaction in an asymmetric manner. Their initial study, the addition of diphenylzinc to aryl alkyl ketones, was based on the same catalyst Noyori previously described for the same reaction using aldehydes as substrates (Scheme 5.1). A further development of this reaction was reported by Yus and co-workers, using a mixture of catalytic amounts of a camphorsulfonamide derivative \[ L_1 \] and an excess of \[ Ti(O\text{Pr})_4 \]. With this catalytic system, depending on the substrate, yields ranging between 25-95% and enantioselectivities up to 89% were obtained (Scheme 5.2).
Enantioselective copper(I)-catalyzed alkylation of aryl alkyl ketones

Later, the groups of Walsh and Yus developed a catalytic system based on bis(sulfonamide) ligand \( \text{L2} \) and \( \text{Ti(O} \text{Pr})_4 \). Ligand \( \text{L2} \) made not only addition of dialkylzinc reagents\(^7-9\) possible, but also diphenylzinc\(^10,11\), divinylzinc\(^12\) and functionalized dialkylzinc reagents could be used. This made the reaction broadly applicable. In addition, the reaction time was reduced to 6-120 h depending on the substrate and zinc reagent (Scheme 5.3). In most cases, aryl alkyl ketones and substituted aryl alkyl ketones were used as substrates, giving tertiary alcohols with yields around 68-99% and enantioselectivities in the range of 46-99%.

In the catalytic systems shown up to now, the major drawback is the application of stoichiometric amounts of \( \text{Ti(O} \text{Pr})_4 \). Therefore, our group was interested to investigate a new catalytic system, in which the amount of the catalytic species is reduced and still the components of the catalytic system are commercially available or easy accessible. A first example of an enantioselective catalytic addition of Grignard reagents to \( \alpha,\beta \)-unsaturated ketones was reported using a combination of \( \text{CuBr-SMe}_2 \) and \( (S,R,z) \)-reverse Josiphos \( \text{L3} \) (Scheme 5.4).\(^13,14\)
Further investigations showed that the same catalytic system can be applied in the reaction with aryl alkyl ketones, to give access to a wide range of benzylic tertiary alcohols. Most of the ketones used in this study are based on an acetophenone scaffold.

5.2 Goal of this study

The goal of the present study is to establish, whether ketones possessing a longer alkyl chain undergo asymmetric copper(I)-catalyzed 1,2-addition with Grignard reagents with high enantioselectivities and yields. In addition, we hope to find a clear correlation between steric and electronic effects of the aryl substituents on the enantioselectivity. Due to the results of the previous studies, the commercially available iso-butylmagnesium bromide was chosen for this investigation, since the enantioselectivity of product 2a is comparable to 2b, and high (Scheme 5.5).
5.3 Results and discussion

In the first set of reactions, the optimized reaction conditions were applied to aryl alkyl ketones possessing an electron withdrawing substituent in various positions. Here, we tried to map the influence of the steric and electronic effects of the substrate on the enantioselectivity. In the first three examples, an acetophenone scaffold was used (Table 5.1, entries 1-3). It turned out that the meta substituted product gave the highest ee (4b, 64%) among the three fluorinated substrates.

A similar observation was made when brominated phenones with a longer alkyl chain were used. The meta substituted product showed the highest ee (4e, 80%) in this set of substrates (entries 4-6). The two substrates 3d and 3g with the bromo substituent in the ortho position, showed only around 10% conversion, and separation of the starting material from the product by column chromatography was not possible. Therefore, no product was isolated for further analysis to determine the ee.

Table 5.1. Aryl alkyl ketones with electron withdrawing substituent on the aromatic ring.

<table>
<thead>
<tr>
<th>entry</th>
<th>Substrate</th>
<th>yield</th>
<th>ee</th>
<th>ratio [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a</td>
<td>4a 36%</td>
<td>rac</td>
<td>11:42:47</td>
</tr>
<tr>
<td>2</td>
<td>3b</td>
<td>4b 37%</td>
<td>64%</td>
<td>12:67:21</td>
</tr>
<tr>
<td>3</td>
<td>3c</td>
<td>4c 24%</td>
<td>27%</td>
<td>9:79:12</td>
</tr>
<tr>
<td>4</td>
<td>3d</td>
<td>4d n.d.</td>
<td>n.d.</td>
<td>17:11:71</td>
</tr>
</tbody>
</table>

- Enantioselective copper(I)-catalyzed alkylation of aryl alkyl ketones
- Table 5.1. Aryl alkyl ketones with electron withdrawing substituent on the aromatic ring.
It is remarkable, that using iso-butylmagnesium bromide as Grignard reagent the meta position of the phenyl ring shows to be favored in terms of enantioselectivity. For the substrates possessing an ortho substituent, a decrease in conversion was observed. In general the ketones used in this study show a lower conversion in comparison to the substrates based on the acetophenone scaffold.

Since the results of this study differ from the results obtained with the acetophenone derivatives, mostly in terms of yield, the influence of the change from 2-ethylbutylmagnesium bromide to iso-butylmagnesium bromide was investigated by performing blank reactions at -78 °C with substrate 1 and both Grignard reagents. The distribution between 1,2-addition product, 1,2-reduction product and starting material was determined by NMR, but no significant difference between the distribution of the compounds was found. Therefore, the increase of the amount of 1,2-reduction product cannot be explained by the change of the Grignard reagent. Instead, the change to ketones with longer alkyl chains, is accompanied with a higher tendency to enolize, which probably causes the lower conversion. To study the possibility that the reactions were just slower, the reaction time was extended to three days.

The isolated yield was obtained after column chromatography. The enantiomeric excess was determined by HPLC; see experimentals. The ratio was determined by $^1$H NMR spectroscopy of the crude product. The approximate ratio was determined from the APT spectrum, due to overlapping signals in the $^1$H NMR spectrum. Standard conditions, but the reaction time was extended to three days.

<table>
<thead>
<tr>
<th>entry</th>
<th>Substrate</th>
<th>yield</th>
<th>$e$</th>
<th>ratio [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>3e</td>
<td>47%</td>
<td>80%</td>
<td>20:50:30</td>
</tr>
<tr>
<td>6</td>
<td>3f</td>
<td>50%</td>
<td>61%</td>
<td>15:68:17</td>
</tr>
<tr>
<td>7</td>
<td>3g</td>
<td>n.d.</td>
<td>n.d.</td>
<td>30:12:58</td>
</tr>
<tr>
<td>8</td>
<td>3h</td>
<td>32%</td>
<td>71%</td>
<td>22:70:8</td>
</tr>
<tr>
<td>9</td>
<td>3h</td>
<td>17%</td>
<td>n.d.</td>
<td>14:52:34</td>
</tr>
</tbody>
</table>

$a$ The isolated yield was obtained after column chromatography. $b$ The enantiomeric excess was determined by HPLC; see experimentals. $c$ The ratio was determined by $^1$H NMR spectroscopy of the crude product. $d$ The approximate ratio was determined from the APT spectrum, due to overlapping signals in the $^1$H NMR spectrum. $e$ Standard conditions, but the reaction time was extended to three days.
days. This was tested with two different substrates (Table 5.1, entry 9; Table 5.2, entries 5). Only for substrate 3l a significant change in conversion was observed, combined with an increase in enantioselectivity. For the other substrate 3h more 1,2-reduction product was formed.

Next, unsubstituted aryl alkyl ketones and acetylfuranes were investigated in terms of conversion and enantioselectivity (Table 5.2). The conversions and isolated yields found are similar to the ones of the substituted aryl ketones, but the enantioselectivity decreased and ranged between 37-65%. Comparing enantioselectivities of products 4i, 4j and 4l it was noticed, that product 4j shows the highest ee among the three products. This result can be explained by the difference in steric bulk between a butyl group and a benzyl group. The ee might also be influenced by π-interactions between the phenyl ring of the benzyl group with the copper. The low conversion of 3l to the desired product is caused by the stable enol-tautomer, which is preferred due to conjugation in the system.

The addition of iso-butyl Grignard reagent to substrate 3k would give a non-chiral compound, therefore ethylmagnesium bromide was added to give the same tertiary alcohol as obtained in entry 1 (Table 5.2, entries 1 and 3). The reaction with ethylmagnesium bromide (entry 3), went to full conversion since in the crude 1H NMR no signals were detected belonging to the starting material. In addition, there was no formation of the 1,2-reduction by-product noticed.

The two furans 3m and 3n both reacted with the iso-butylmagnesium bromide (entries 6 and 7), but product 4m was found as a racemic compound whereas 4n shows a relatively high ee of 65% (being in the same range as the substituted phenones).
Table 5.2. Asymmetric 1,2-addition to unsubstituted alkyl aryl and heteroaryl ketones.

<table>
<thead>
<tr>
<th>entry</th>
<th>Substrate</th>
<th>yield</th>
<th>ee</th>
<th>ratio [%] 3:4:5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3i</td>
<td>4i 39%</td>
<td>48%</td>
<td>16:62:22^f</td>
</tr>
<tr>
<td>2</td>
<td>3j</td>
<td>4j 32%</td>
<td>56%</td>
<td>19:66:15^f</td>
</tr>
<tr>
<td>3</td>
<td>3k</td>
<td>4k 67%^f</td>
<td>37%</td>
<td>0:100:0</td>
</tr>
<tr>
<td>4</td>
<td>3l</td>
<td>4l 12%</td>
<td>40%</td>
<td>35:29:36</td>
</tr>
<tr>
<td>5^f</td>
<td>3l</td>
<td>4l 19%</td>
<td>52%</td>
<td>6:56:38</td>
</tr>
<tr>
<td>6</td>
<td>3m</td>
<td>4m 35%</td>
<td>Rac</td>
<td>37:55:08</td>
</tr>
<tr>
<td>7</td>
<td>3n</td>
<td>4n 21%</td>
<td>65%</td>
<td>51:38:11</td>
</tr>
</tbody>
</table>

^a The isolated yield was obtained after column chromatography. ^b The enantiomeric excess was determined by HPLC. ^c The ratio was determined by 1H NMR spectroscopy of the crude product. ^d The approximate ratio was determined from the APT spectrum. ^e Ethylmagnesium bromide was added. ^f Standard condition, but the reaction time was extended to three days.

Additionally, ketones with more steric hindrance and biaryl ketones were studied as well (Scheme 5.6). The two ketones 3o and 3p showed some conversion, but too little to isolate the products and determine the ee. For the substrates 3q and 3r no reaction was observed. This indicates that an increase of the steric bulk next to the C=O double bond prevents the reaction. An exception was substrate 3s, which gave selectively the 1,2-reduction product. The two biaryl ketones 3t and 3u were investigated, to see if chiral induction is possible with similar substituents next to the carbonyl double bond. However, both substrates showed no reactivity at all. To
Enantioselective copper(I)-catalyzed alkylation of aryl alkyl ketones

broaden the scope of the reaction using heteroaromatic substrates, ketone 3v was tested in the reaction as an example, but no product formation was observed.

Scheme 5.6. Bulky substrates in the 1,2-addition.

5.4 Conclusion

The results of this study show, that several aryl alkyl ketones with alkyl chains longer than methyl undergo the 1,2-addition using our new catalytic system. However, enolization and 1,2-reduction become considerable competitors for the desired 1,2-addition. In addition to acetylthiophene, also acetylfurans showed desired reactivity in the 1,2-addition.

In general, for phenones, aryl alkyl ketones with an unsubstituted phenyl ring, a decrease in enantioselectivity was observed and in addition the apparent conversion was far from complete after the standard reaction time. During a longer reaction time no significant increase of $ee$ was observed. Remarkably, for ketone 3h a bit more side product was formed, whereas for ketone 3l more starting material was converted to the desired product. This does not match with enolization of the starting material, as one would expect the enolate to be stable under the reaction conditions.

The results of reactions with substituted aryl alkyl ketones showed, that the substitution pattern on the phenyl ring has an influence on the enantioselectivity. Substrate 3a, with a fluoro substituent in the ortho position, produces a racemate, and the substrates 3c and 3e possessing a substituent in meta position showed the highest $ee$’s.

A limitation in terms of substrate scope was found, when biaryl ketones and bulkier alkyl groups were used. Here, 1,2-addition was hardly observed. In the future more
ligands need to be screened to adjust the catalytic system in such a way, that addition of linear Grignard reagents to aryl alkyl ketones will be possible. This means the bulkiness of the ligand will influence the differentiation of the two faces of the carbonyl double bond.

5.5 Experimental

For general information see experimental of chapter 2.

5.5.1 Synthesis of the ketones 3d, 3g

**General procedure for the synthesis of secondary alcohols S1a, b**

2-bromobenzaldehyde (1 eq) was dissolved in THF (0.8 mL/mmol) and cooled with an ice bath to 0 °C. To this the Grignard reagent (1.7 eq) was added dropwise. The ice bath was removed and the reaction mixture was stirred at rt for 16 h. The reaction was quenched by adding saturated aq. NH₄Cl. 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.

Purification by column chromatography afforded S1a and S1b as colorless oil.

For S1a the Grignard reagent was purchased from Aldrich as a 3 M solution in diethyl ether.

For S1b the Grignard reagent was prepared as follow: magnesium (2.43 g, 100 mmol, 2.5 eq) was activated with an iodine crystal and 5 mL diethyl ether was added. To this was added dropwise a solution of 1-bromopropane (4.91 g, 40 mmol, 1.7 eq) in 10 mL diethyl ether to keep the reaction mixture refluxing. The reaction mixture was stirred for 18 h at rt before further use.

1-(2-bromophenyl)propan-1-ol (S1a)

Following the general procedure, 2.40 g (13 mmol) 2-bromobenzaldehyde was reacted with 11 mL ethylmagnesium bromide to give 1.65 g S1a (7.7 mmol, 59%) after column chromatography (SiO₂, pentane/diethyl ether 9:1), Rf = 0.35 in pentane/diethyl ether, 9:1). ³H NMR (400.0 MHz, CDCl₃): δ ppm 7.51 (m, 2H), 7.32 (m, 1H), 7.21 (m, 1H), 5.00 (q,
Enantioselective copper(I)-catalyzed alkylation of aryl alkyl ketones

1H), 2.25 (s, 1H), 1.82 (m, 1H), 1.68 (m, 1H), 0.99 (t, 3H). 13C NMR (100.6 MHz, CDCl3): δ ppm 143.5 (C), 132.5 (CH), 128.6 (CH), 127.6 (CH), 127.3 (CH), 122.1 (C), 74.1 (CH), 30.5 (CH2), 10.0 (CH3). HRMS (APCI+): m/z [M-H2O]+ calcd for C9H10Br: 196.9960; found: 196.9959.

1-(2-bromophenyl)butan-1-ol (S1b)

Following the general procedure, 4.35 g (23 mmol) 2-bromobenzaldehyde was reacted with 15 mL propylmagnesium bromide to give 2.79 g S1b (12 mmol, 52%) after column chromatography (SiO2, pentane/diethyl ether 9:1, Rf = 0.46 in pentane/diethyl ether, 9:1). 1H NMR (400.0 MHz, CDCl3): δ ppm 7.51 (m, 2H), 7.31 (m, 1H), 7.10 (m, 1H), 5.06 (m, 2H), 1.68 (m, 2H), 1.53-1.39 (m, 2H), 0.96 (t, 3H). 13C NMR (100.6 MHz, CDCl3): δ ppm 143.9 (C), 132.6 (CH), 128.6 (CH), 127.7 (CH), 127.3 (CH), 122.0 (C), 72.6 (CH), 39.8 (CH2), 19.0 (CH2), 13.9 (CH3). HRMS (APCI+): m/z [M-H2O]+ calcd for C10H12OBr: 211.0017; found: 211.0117.

Oxidation to ketones 3d, 3g

1-(2-bromophenyl)propan-1-one (3d)

S1a (724 mg, 3.4 mmol, 1 eq) was dissolved in dry CH2Cl2. At 0 °C (ice bath) Dess-Martin periodinane (2.0 g, 4.7 mmol, 1.4 eq) and NaHCO3 (566 mg, 6.7 mmol, 2 eq) were added. The reaction was subsequently stirred at rt for 2 h (until TLC indicated consumption of the starting material). The excess of oxidant was destroyed by adding 2-propanol (2 mL), the mixture was poured into 100 mL pentane/diethyl ether (9:1) (Rf = 0.60 pentane/diethyl ether, 9:1) and allowed to stand for 30 min at rt. The mixture was directly loaded on to a silica column. After purification 3d (722 mg, 3.4 mmol, 100%) was isolated. 1H NMR (400.0 MHz, CDCl3): δ ppm 7.69 (d, 1H), 7.36 (d, 1H), 7.28 (m, 2H), 2.93 (q, 2H), 1.21 (t, 3H). 13C NMR (100.6 MHz, CDCl3): δ ppm 205.0 (C), 142.0 (C), 133.5 (CH), 131.5 (CH), 128.1 (CH), 127.4 (CH), 118.5 (C), 36.0 (CH2), 8.1 (CH3). HRMS (ESI+): m/z [M+H]+ calcd for C9H10OBr: 212.9909; found: 212.9910.
1-(2-bromophenyl)butan-1-one (3g)

S1b (2.00 g, 8.7 mmol) was dissolved in dry CH₂Cl₂. At 0 °C (ice bath) 2-iodoxybenzoic acid (6.25 g, 14.7 mmol, 1.7 eq) and NaHCO₃ (1.47 g, 17.5 mmol, 2 eq) were added. The reaction was then stirred at rt for 16 h (until TLC indicated consumption of the starting material). The solvent of the reaction mixture was evaporated. The crude product was purified by column chromatography (SiO₂, pentane/diethyl ether 9:1, Rf = 0.33 in pentane/diethyl ether, 9:1) to give 3g as colorless oil (0.75 g, 3.3 mmol, 38%). ¹H NMR (400.0 MHz, CDCl₃): δ ppm 7.69 (d, 1H), 7.36 (d, 1H), 7.28 (m, 2H), 2.93 (q, 2H), 1.21 (t, 3H). ¹³C NMR (100.6 MHz, CDCl₃): δ ppm 204.5 (C), 142.1 (C), 133.6 (CH), 131.3 (CH), 128.2 (CH), 127.3 (CH), 118.5 (C), 44.6 (CH₂), 17.6 (CH₂), 13.7 (CH₃). HRMS (ESI⁺): m/z [M+H] calcd for C₁₀H₁₂OBr: 227.0066; found: 227.0066.

5.5.3 General procedure for the copper-catalyzed 1,2-addition to ketones

CuBr·SmMe₂ (0.015 mmol, 5 mol%) and (S,R)-reverse Josiphos (L₃) (0.018 mmol, 6 mol%) were dissolved in dry MTBE (2 mL) and stirred at rt for 15 min. To this mixture was added the corresponding ketone (0.3 mmol, 1 eq) in 2 mL dry MTBE. Then the mixture was cooled to −78 °C. After stirring for 15 min at −78 °C the corresponding Grignard reagent (0.36 mmol, 1.2 eq) was added within 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. NH₄Cl. After the reaction mixture reached rt, the layers were separated and the water layer was extracted three times with CH₂Cl₂. The combined organic layers were dried over MgSO₄, filtered and the filtrate was concentrated in vacuo. From the crude product a sample was taken for GC-MS and NMR 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.
Enantioselective copper(I)-catalyzed alkylation of aryl alkyl ketones

2-(2-fluorophenyl)-4-methylpentan-2-ol (4a)

The title compound was prepared from ketone 3a following the general procedure. Purification by column chromatography (SiO$_2$, pentane/diethyl ether 9:1, $R_f = 0.37$ in pentane/diethyl ether, 9:1) afforded 4a as a light yellow oil (21.6 mg, 0.110 mmol, 36%, rac). $^1$H NMR (400.0 MHz, CDCl$_3$): $\delta$ ppm 7.29 (m, 1H), 7.19 (m, 1H), 7.16 (m, 1H), 6.92 (m, 1H), 3.48 (m, 1H), 1.74 (m, 2H), 1.61 (m, 1H), 1.54 (s, 3H), 0.89 (d, 3H), 0.75 (d, 3H). $^{13}$C NMR (100.6 MHz, CDCl$_3$): $\delta$ ppm 164.1 (C), 151.1 (C), 129.5 (CH), 121.4 (CH), 113.1 (CH), 112.1 (CH), 75.0 (C), 52.6 (CH$_2$), 31.4 (CH$_3$), 24.6 (CH$_2$), 24.6 (CH$_2$), 24.3 (CH$_3$). Optical rotation $[\alpha]_D^{20} = -5.7$ (c = 0.1, CHCl$_3$). HRMS (APCI+): m/z [M-HF]$^+$ calc for C$_{12}$H$_{17}$O: 177.1273; found: 177.1269. The enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel AD-H column, n-heptane/i-PrOH 99:1, 40 °C isotherm, detection at 206 nm, retention time (min): 14.9 and 15.4.

2-(3-fluorophenyl)-4-methylpentan-2-ol (4b)

The title compound was prepared from ketone 3b following the general procedure. Purification by column chromatography (SiO$_2$, pentane/diethyl ether 9:1, $R_f = 0.43$ in pentane/diethyl ether, 9:1) afforded 4b as a light yellow oil (21.6 mg, 0.110 mmol, 36%, 64% ee). $^1$H NMR (400.0 MHz, CDCl$_3$): $\delta$ ppm 7.31 (m, 1H), 7.19 (m, 1H), 7.16 (m, 1H), 6.92 (m, 1H), 3.48 (m, 1H), 1.77 (m, 2H), 1.61 (m, 1H), 1.54 (s, 3H), 0.89 (d, 3H), 0.75 (d, 3H). $^{13}$C NMR (100.6 MHz, CDCl$_3$): $\delta$ ppm 164.1 (C), 151.1 (C), 129.5 (CH), 121.4 (CH), 113.1 (CH), 112.1 (CH), 75.0 (C), 52.6 (CH$_2$), 31.4 (CH$_3$), 24.6 (CH$_2$), 24.6 (CH$_2$), 24.3 (CH$_3$). Optical rotation $[\alpha]_D^{20} = -1.2$ (c = 0.9, CHCl$_3$). HRMS (APCI+): m/z [M-HF]$^+$ calc for C$_{12}$H$_{17}$O: 177.1274; found: 177.1275. The enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel AS-H column, n-heptane/i-PrOH 100:0, 40 °C isotherm, detection at 207 nm, retention time (min): 16.8 (major) and 18.3 (minor).

2-(4-fluorophenyl)-4-methylpentan-2-ol (4c)

The title compound was prepared from ketone 3c following the general procedure. Purification by column chromatography (SiO$_2$, pentane/diethyl ether 9:1, $R_f = 0.53$ in pentane/diethyl ether, 9:1) afforded 4c as a light yellow oil (13.9 mg, 0.071 mmol, 24%, 32% ee). $^1$H NMR (400.0 MHz, CDCl$_3$): $\delta$ ppm 7.40 (q, 2H), 7.01 (t, 2H), 1.74 (m, 2H), 1.60 (m, 2H), 1.54 (s, 3H), 0.88 (d, 3H), 0.76 (d, 3H). $^{13}$C NMR (100.6 MHz, CDCl$_3$): $\delta$ ppm 162.7 (C), 144.0 (C), 126.5 (CH), 126.4 (CH), 114.8 (CH), 114.6 (CH), 75.0 (C), 52.9 (CH$_2$), 31.5 (CH$_3$), 30.3 (CH), 24.4 (CH$_3$), 24.3 (CH$_3$). Optical rotation $[\alpha]_D^{20} = -6.3$ (c =
0.2, CHCl₃). HRMS (APCI+): m/z [M-HF]⁺ calcd for C₁₂H₁₇O: 177.1273; found: 177.1274. The enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel AD-H column, n-heptane/i-PrOH 99:1, 40 °C isotherm, detection at 207 nm, retention time (min): 22.2 (major) and 23.1 (minor).

3-(3-bromophenyl)-5-methylhexan-3-ol (4e)

The title compound was prepared from ketone 3e following the general procedure. Purification by column chromatography (SiO₂, pentane/diethyl ether 9:1, Rᵣ = 0.49 in pentane/diethyl ether, 9:1) afforded 4e as a light yellow oil (38.2 mg, 0.141 mmol, 47%, 80% ee). ¹H NMR (400.0 MHz, CDCl₃): δ ppm 7.56 (m, 1H), 7.35 (m, 1H), 7.28 (m, 1H), 7.19 (m, 1H), 1.71 (m, 2H), 1.59 (m, 2H), 1.54 (s, 1H), 1.49 (m, 1H), 0.91 (d, 3H), 0.74 (d, 3H), 0.71 (t, 3H). ¹³C NMR (100.6 MHz, CDCl₃): δ ppm 148.8 (C), 129.5 (CH), 129.2 (CH), 128.7 (CH), 124.1 (CH), 122.4 (C), 77.5 (C), 51.4 (CH₂), 36.2 (CH₂), 24.5 (CH₃), 24.3 (CH₃), 24.1 (CH), 7.5 (CH₃). Optical rotation [α]$_{D}^{20}$ = -2.4 (c = 1.0, CHCl₃). HRMS (ESI⁻): m/z [M-H⁻] calcd for C₁₃H₁₈OBr: 271.0516; found: 271.0513. The enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel OD-H column, n-heptane/i-PrOH 99:1, 40 °C isotherm, detection at 203 nm, retention time (min): 12.48 (major) and 13.01 (minor).

3-(4-bromophenyl)-5-methylhexan-3-ol (4f)

The title compound was prepared from ketone 3f following the general procedure. Purification by column chromatography (SiO₂, pentane/diethyl ether 9:1, Rᵣ = 0.54 in pentane/diethyl ether, 9:1) afforded 4f as a light yellow oil (41.0 mg, 0.151 mmol, 50%, 61% ee). ¹H NMR (400.0 MHz, CDCl₃): δ ppm 7.37 (dd, 2H), 7.19 (dd, 2H), 1.71 (m, 2H), 1.58 (m, 1H), 1.51 (s, 1H), 1.46 (m, 2H), 0.83 (d, 3H), 0.66 (d, 3H), 0.63 (t, 3H). ¹³C NMR (100.6 MHz, CDCl₃): δ ppm 145.2 (C), 131.0 (2 x CH), 127.4 (2 x CH), 120.0 (C), 77.5 (C), 51.4 (CH₂), 36.7 (CH₂), 24.6 (CH₃), 24.3 (CH₃), 24.1 (CH), 7.5 (CH₃). Optical rotation [α]$_{D}^{20}$ = -1.7 (c = 1.0, CHCl₃). HRMS (ESI⁻): m/z [M-H⁻] calcd for C₁₃H₁₈OBr: 271.0511; found: 271.0510. The enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel OD-H column, n-heptane/i-PrOH 99:1, 40 °C, detection at 222 nm, retention time (min): 12.59 (major) and 13.41 (minor).
The title compound was prepared from ketone 3h following the general procedure. Purification by column chromatography (SiO$_2$, pentane/diethyl ether, 9:1, R$_f$ = 0.46 in pentane/diethyl ether, 9:1) afforded 4h as a light yellow oil (32.0 mg, 0.096 mmol, 32%, 71% ee). $^1$H NMR (400.0 MHz, CDCl$_3$): $\delta$ ppm 7.42 (d, 2H), 7.19 (m, 5H), 6.90 (m, 2H), 3.10 (d, 1H), 2.99 (d, 1H), 1.94 (dd, 1H), 1.68 (dd, 1H), 1.52 (m, 2H), 0.88 (d, 3H), 0.69 (d, 3H). $^{13}$C NMR (100.6 MHz, CDCl$_3$): $\delta$ ppm 145.1 (C), 135.2 (C), 130.9 (2 x CH), 130.6 (2 x CH), 128.2 (2 x CH), 127.5 (2 x CH), 126.8 (CH) 120.2 (C), 77.2 (C), 50.8 (CH$_2$), 50.7 (CH$_2$), 24.6 (CH$_3$), 24.5 (CH$_3$), 24.0 (CH). Optical rotation $[\alpha]_D^{20} = -47.9$ (c = 1.1, CHCl$_3$). HRMS (APCI+): m/z [M-OH]$^+$ calc for C$_{18}$H$_{20}$Br: 315.0743; found: 315.0732. The enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel OD-H column, n-hexane/i-PrOH 99:1, 40 °C, detection at 190 nm, retention time (min): 16.17 (major) and 17.30 (minor).

5-methyl-3-phenylhexan-3-ol (4i)

The title compound was prepared from ketone 3i following the general procedure. Purification by column chromatography (SiO$_2$, pentane/diethyl ether, 9:1, R$_f$ = 0.28 in pentane/diethyl ether, 9:1) afforded 4i as a light yellow oil (22.6 mg, 0.117 mmol, 39%, 48% ee). $^1$H NMR (400.0 MHz, CDCl$_3$): $\delta$ ppm 7.39-7.30 (m, 4H), 7.21 (m, 1H), 1.82 (m, 2H), 1.68 (m, 2H), 1.54 (m, 1H), 1.43 (s, 1H), 0.90 (d, 3H), 0.73 (t, 3H) 0.68 (d, 3H). $^{13}$C NMR (100.6 MHz, CDCl$_3$): $\delta$ ppm 146.1 (C), 127.9 (2 x CH), 126.1 (CH), 125.4 (2 x CH), 77.7 (C), 51.4 (CH$_2$), 36.6 (CH$_2$), 24.5 (CH$_3$), 24.4 (CH$_3$), 24.1 (CH), 7.6 (CH$_3$). Optical rotation $[\alpha]_D^{20} = 3.3$ (c = 1.1, CHCl$_3$). HRMS-ESI+: m/z [M]$^+$ calc for C$_{13}$H$_{18}$OBr: 270.0619; found: 271.0511. The enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel OD-H column, n-hexane/i-PrOH 100:0, 40 °C, detection at 205 nm, retention time (min): 20.97 (major) and 23.34 (minor).

2-methyl-4-phenylheptan-4-ol (4j)

The title compound was prepared from ketone 3j following the general procedure. Purification by column chromatography (SiO$_2$, pentane/diethyl ether, 9:1, R$_f$ = 0.31 in pentane/diethyl ether, 9:1) afforded 4j as a light yellow oil (20.1 mg, 0.097 mmol, 32%, 56% ee). $^1$H NMR (400.0 MHz, CDCl$_3$): $\delta$ ppm 7.39-7.30 (m, 4H), 7.21 (m, 1H), 1.80 (m, 2H), 1.64 (m, 2H), 1.57 (m, 1H), 1.43 (s, 1H), 1.27 (m, 2H), 0.90 (d, 3H), 0.83 (t, 3H), 0.69 (d, 3H). $^{13}$C NMR (100.6 MHz, CDCl$_3$): $\delta$ ppm 146.5 (C), 127.9 (2 x CH),
5-methyl-3-phenylhexan-3-ol (4k)

The title compound was prepared from ketone 3k following the general procedure. Purification by column chromatography (SiO\textsubscript{2}, pentane/diethyl ether 9:1, R\textsubscript{f} = 0.51 in pentane/diethyl ether, 9:1) afforded 4k as a light yellow oil (39.2 mg, 0.204 mmol, 68%, 37\% ee).

\(^1\)H NMR (400.0 MHz, CDCl\textsubscript{3}): \(\delta\) ppm 7.39-7.31 (m, 4H), 7.21 (m, 1H), 1.83 (m, 3H), 1.61 (m, 1H), 1.62 (s, 1H), 1.55 (m, 1H), 0.90 (d, 3H), 0.83 (t, 3H), 0.69 (d, 3H).

\(^13\)C NMR (100.6 MHz, CDCl\textsubscript{3}): \(\delta\) ppm 146.1 (C), 127.9 (2 x CH), 126.1 (CH), 125.4 (2 x CH), 77.7 (C), 51.4 (CH\textsubscript{2}), 36.6 (CH\textsubscript{2}), 24.6 (CH\textsubscript{3}), 24.4 (CH\textsubscript{3}), 24.1 (CH), 7.6 (CH\textsubscript{3}). Optical rotation \([\alpha]\textsubscript{D}\textsubscript{20} = 2.6 (c = 0.5, CHCl\textsubscript{3})

HRMS (ESI\textsuperscript{-}): \(m/z\) [M-H]\textsuperscript{+} calcd for C\textsubscript{14}H\textsubscript{21}O: 205.1586; found: 205.1587. The enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel OD-H column, n-heptane/i-PrOH 100:0, 40 °C, detection at 208 nm, retention time (min): 20.34 (major) and 22.02 (minor).

4-methyl-1,2-diphenylpentan-2-ol (4l)

The title compound was prepared from ketone 3l following the general procedure. Purification by column chromatography (SiO\textsubscript{2}, pentane/diethyl ether 9:1, R\textsubscript{f} = 0.59 in pentane/diethyl ether, 9:1) afforded 4l as a light yellow oil (20.9 mg, 0.082 mmol, 27%, 40\% ee).

\(^1\)H NMR (400.0 MHz, CDCl\textsubscript{3}): \(\delta\) ppm 7.31 (m, 4H), 7.23 (m, 1H), 7.18 (m, 3H), 6.90 (m, 2H), 3.14 (d, 1H), 3.01 (d, 1H), 1.97 (dd, 1H), 1.69 (dd, 1H), 1.47 (m, 2H), 0.80 (d, 3H), 0.61 (d, 3H).

\(^13\)C NMR (100.6 MHz, CDCl\textsubscript{3}): \(\delta\) ppm 145.9 (C), 136.1 (C), 130.7 (2 x CH), 129.9 (CH), 129.0 (CH), 128.0 (2 x CH), 127.8 (2 x CH), 126.6 (CH), 126.2 (CH), 77.2 (C), 50.9 (CH\textsubscript{2}), 50.8 (CH\textsubscript{2}), 24.6 (CH\textsubscript{3}), 24.3 (CH\textsubscript{3}), 24.0 (CH). Optical rotation \([\alpha]\textsubscript{D}\textsubscript{20} = -34.9 (c = 0.4, CHCl\textsubscript{3})

HRMS (APCI\textsuperscript{+}): \(m/z\) [M-OH]\textsuperscript{+} calcd for C\textsubscript{18}H\textsubscript{21}: 237.1638; found: 237.1634. The enantiomeric ratio was determined by chiral HPLC analysis, Chiralpak OJ-H column, n-heptane/i-PrOH 99:1, 40 °C, detection at 209 nm, retention time (min): 11.96 (minor) and 12.48 (major).
2-(furan-2-yl)-4-methylpentan-2-ol (4m)

The title compound was prepared from ketone 3m following the general procedure. Purification by column chromatography (SiO\textsubscript{2}, pentane/diethyl ether 9:1, \(R_f = 0.18\) in pentane/diethyl ether, 9:1) afforded 4m as a light yellow oil (17.7 mg, 0.105 mmol, 35%, rac). \(^1\)H NMR (400.0 MHz, CDCl\textsubscript{3}): \(\delta\) ppm 7.34 (m, 1H), 6.30 (m, 1H), 6.19 (dd, 1), 1.91 (s, 1H), 1.78 (m, 2H), 1.64 (m, 1H), 1.55 (s, 3H), 0.83-0.79 (dd, 9H). \(^1\)C NMR (100.6 MHz, CDCl\textsubscript{3}): \(\delta\) ppm 159.8 (C), 141.2 (CH), 110.1 (CH), 104.3 (CH), 71.8 (C), 50.3 (CH\textsubscript{2}), 27.3 (CH\textsubscript{3}), 24.5 (CH\textsubscript{3}), 24.1 (CH\textsubscript{3}), 23.9 (CH). HRMS (APCI\textsuperscript{+}): \textit{m/z} [M-HO]\textsuperscript{+} calcd for C\textsubscript{10}H\textsubscript{15}O: 151.1117; found: 151.1118.

4-methyl-2-(5-methylfuran-2-yl)pentan-2-ol (4n)

The title compound was prepared from ketone 3n following the general procedure. Purification by column chromatography (SiO\textsubscript{2}, pentane/diethyl ether 9:1, \(R_f = 0.68\) in pentane/diethyl ether, 1:1) afforded 4n as a light yellow oil (11.6 mg, 0.064 mmol, 21%, 65% ee). \(^1\)H NMR (400.0 MHz, CDCl\textsubscript{3}): \(\delta\) ppm 6.04 (d, 1H), 5.87 (m, 1H), 2.27 (s, 3H), 1.76 (m, 2H), 1.64 (m, 1H), 1.53 (s, 3H), 0.86 (d, 3H), 0.80 (d, 3H). \(^1\)C NMR (100.6 MHz, CDCl\textsubscript{3}): \(\delta\) ppm 158.0 (C), 150.8 (C), 105.9 (CH), 104.9 (CH), 71.6 (C), 50.2 (CH\textsubscript{2}), 27.0 (CH\textsubscript{3}), 24.5 (CH\textsubscript{3}), 23.9 (CH), 13.5 (CH\textsubscript{3}). Optical rotation \([\alpha]_D^{20\circ} = -1.4\) (c = 0.6, CHCl\textsubscript{3}). HRMS (APCI\textsuperscript{+}): \textit{m/z} [M-OH]\textsuperscript{+} calcd for C\textsubscript{11}H\textsubscript{17}O: 165.1274; found: 165.1272. The enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel AD-H column, \(n\)-heptane/i-PrOH 99:1, 40 °C, detection at 209 nm, retention time (min): 22.12 (minor) and 22.93 (major).
5.6 References