Total syntheses of (–)-Borrelidin and (–)-Doliculide and the development of the catalytic asymmetric addition of Grignard reagents to ketones
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Chapter 5

Copper-Catalyzed Asymmetric 1,2-Addition of Grignard Reagents to Aromatic Ketones

In this chapter, the first copper-catalyzed asymmetric 1,2-addition of Grignard reagents to aromatic ketones is described. This method leads to tertiary benzylic alcohols in up to 97% yield and 98% ee.

Parts of this chapter have been published:
5.1 Introduction

Tertiary alcohols occur ubiquitous in natural products and pharmaceutical compounds, and methods for the enantioselective preparation of their chiral congeners are therefore a necessity. Whereas the synthesis of enantiopure secondary alcohols is well established due to mature strategies like asymmetric hydrogenation of ketones with transition-metals and enzymes, and dynamic kinetic resolution of the corresponding racemates, these strategies do not apply for tertiary alcohols. Even the resolution of racemic tertiary alcohols with lipases or esterases is mostly not efficient. The most straightforward method to prepare chiral enantiopure tertiary alcohols would be the catalytic asymmetric addition of organometallic reagents to ketones. For the addition of alkyl groups, this notion has led to several studies in which dialkylzincs and organotitanium reagents were used effectively (Scheme 1).

Scheme 1: 1,2-addition of diethyl zinc reagents to ketones

In stark contrast, the only examples of enantioselective reactions with the direct use of organomagnesium reagents use stoichiometric chiral ligands (Scheme 2a). Nevertheless, there are advantages in the use of common monoalkylmagnesium halide reagents as opposed to dialkylzinc compounds, most notably the ready availability of inexpensive Grignard reagents, and the transfer of all the alkyl groups of the organometallic compound. The advantages of monoalkylmagnesium halides prompted us to search for a highly enantioselective family of ligands for this asymmetric transformation. Several factors complicate the control of stereochemistry in this organometallic-based transformation and cause unpredictable behavior. Recently Ishihara has reported a catalytic non-asymmetric addition of Grignard reagents to ketones using Zn(II) salts as catalyst (Scheme 1b).
Asymmetric 1,2-addition of Grignard reagents to aromatic ketones

Asymmetric 1,2-addition of Grignard reagents to ketones with stoichiometric amount of ligand, catalytic non-asymmetric addition of Grignard reagents to ketones

When considering the addition of organometallic reagents to ketones one must take into account the significantly diminished reactivity compared to aldehydes and consequently extended reaction times. The use of highly reactive organomagnesium reagents can overcome this problem, however it is often accompanied by the formation of undesired by-products via enolisation and competitive reduction via \( \beta \)-H transfer (see for a detailed discussion chapter 4). Additional difficulties in using Grignard reagents with ketones are related to a decreased enantiodiscrimination due to the smaller steric and electronic differences between the two substituents on the carbonyl group.

The group of Aggarwal has developed a method that converts chiral enantiopure secondary alcohols into tertiary alcohols with very high enantioselectivities (Scheme 3).

This process shows broad scope in terms of both secondary alcohols, although it seems limited to benzyllic alcohols, and boranes or boronic esters used. As a result it allows access to a broad range of tertiary alcohols. Furthermore, either enantiomer of a tertiary alcohol can be obtained with high enantioselectivity from a single enantiomer of the corresponding secondary alcohol, depending on whether a borane or boronic ester is used. This method uses a very different concept than usual methods to prepare tertiary alcohols, but it
requires several steps and availability of enantiopure secondary alcohols as the starting material.

Scheme 3: Chiral enantiopure tertiary alcohols from chiral enantiopure secondary alcohols
Asymmetric 1,2-addition of Grignard reagents to aromatic ketones

Development of a catalytic enantioselective method for the synthesis of tertiary alcohols using organomagnesium reagents has proven elusive until now. In this chapter, we describe that the addition of Grignard reagents to ketones, an archetypical reaction in organic chemistry, can now be carried out in a catalytic asymmetric manner (Scheme 4). The use of a copper catalyst based on a chiral Josiphos-type diphosphine ligand, in t-butyl methyl ether, provides excellent yields and enantiomeric excesses (>95%) in the addition of branched alkyl Grignard reagents to arylalkyl ketones. In the previous chapter (chapter 4) we have shown that, counterintuitively, copper-diphosphine catalysts can be used for the enantioselective 1,2-addition of Grignard reagents to enones. Although the conjugated double bond is thought to play a major role in the course of that reaction, we nevertheless used this catalyst system to study the unprecedented asymmetric addition of Grignard reagents to arylalkyl ketones.

Scheme 4: Catalytic asymmetric addition of Grignard reagents to arylalkyl ketones

5.2 Results and discussion

Initial experiments were carried out using acetophenone as the substrate and CuBr•SMe₂ as the metal precursor. In the absence of ligand, the reaction with 2-ethyl-butylmagnesium bromide in t-butyl methyl ether at various temperatures provided only a small amount of the addition product. The main products were phenethyl alcohol due to Meerwein-Ponndorf-Verley reduction, next to remaining starting material, probably due to enolisation. A subsequent ligand screening involved a variety of chiral ligands including monodentate phosphoramidites and bidentate diphosphines. Josiphos-type ligand L₁ turned out to be far superior both in terms of yield and enantioselectivity, a maximum ee of 82% with an excellent 96% yield being obtained at –78 °C (Table 1, entry 1). This indicates that the catalyst has a particularly high turn-over frequency and outcompetes the uncatalyzed addition reaction, as well as reduction and enolisation, at this temperature.
Table 1: Catalytic asymmetric 1,2-addition of 2-ethyl-butylmagnesium bromide to arylalkyl ketones.

<table>
<thead>
<tr>
<th>Entry</th>
<th>1</th>
<th>2, ee (yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1a</td>
<td>2a, 82 (96)</td>
</tr>
<tr>
<td>2b</td>
<td>1b</td>
<td>2b, 76 (85)</td>
</tr>
<tr>
<td>3</td>
<td>1c</td>
<td>2c, 76 (93)</td>
</tr>
<tr>
<td>4</td>
<td>1d</td>
<td>2d, 76 (95)</td>
</tr>
</tbody>
</table>
Asymmetric 1,2-addition of Grignard reagents to aromatic ketones

5e

6

7e

8e

9

137
Asymmetric 1,2-addition of Grignard reagents to aromatic ketones

15

16

17'

18

19'

139
We were delighted to see that this positive outcome is representative for a broad spectrum of substituted acetophenones (Table 1). Upon addition of the same Grignard reagent 2-ethyl-butyldimagnesium bromide, good to excellent ee’s were obtained in combination with high isolated yields. Surprisingly, no clear trends are observed that relate steric and electronic effects of the substituents to enantioselectivity. Para and meta substituents have small but significant effects on the ee and, remarkably, a bromo substituent does not suffer from metal-halogen exchange. Mavericks are 3-trifluoromethyl acetophenone 1i with an excellent ee of 96% and 3-methoxyacetophenone 1h with a decreased yield and an ee of 54%. Remarkable are the excellent enantioselectivities obtained for 3,4-dichloroacetophenone (1n, 96%), 3,5-difluoroacetophenone (1o, 92%) and especially 3,5-difluoromethyl acetophenone (1p, 98%). Also an ortho-bromo substituent is well tolerated (1m, 95% ee) although the yield decreases.

A small extension of the study shows that the reaction is limited neither to methyl-substituted ketones nor to phenyl-substituted ketones. Thus, trifluoromethyl propiophenone 1k gives upon addition an ee of 84% (entry 11), comparable to acetophenone (ee 82%, entry 1) but lower than trifluoromethyl acetophenone 1i (ee 96%, entry 9). 2-Acetonaphthone 1q gives a diminished enantioselectivity but
1-acetonaphthone 1r an excellent ee of 95% (entries 17 and 18). Even 2-acetoantracenone 1s is a suitable substrate for the reaction (80% ee, 88% yield). Also heteroaromatic substituents are allowed as shown with 2-thiophenyl methyl ketone 1t. The addition to alkyl, alkyl ketones (not depicted) failed in terms of erantioselectivity and also the addition of phenylmagnesium bromide afforded racemic product (2u, entry 21).

Having established the broad substrate scope, the scope in terms of Grignard reagents was studied (Table 2), using 1p as the substrate. In order to obtain high enantioselectivities, branched, e.g. more bulky, Grignard reagents are required. Ethylmagnesium bromide gives a low 22% ee (methylmagnesium bromide is inactive), butenylmagnesium bromide already 44% and via phenylethylmagnesium bromide (68% ee) it reaches 95% ee with isobutylmagnesium bromide (entries 1-3). The yields are invariably excellent. Very rewarding as well is the addition of 2-ethyl-butylmagnesium bromide, 2-ethyl-hexylmagnesium bromide and cyclohexylmethylmagnesium bromide each affording the corresponding alcohol in 98% ee (entries 4-6).

Table 2: Catalytic asymmetric 1,2-addition of Grignard reagents to 3,5-ditrifluoromethyl acetophenone, 1p

<table>
<thead>
<tr>
<th>Entry</th>
<th>RMgBr</th>
<th>ee (yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MgBr</td>
<td>22 (94)</td>
</tr>
<tr>
<td>2</td>
<td>MeBr</td>
<td>44 (92)</td>
</tr>
</tbody>
</table>
A special note deserves the addition of trimethylsilylmethylmagnesium bromide, because the resulting 1,2-addition product is expedient for further functionalization. To our delight, the addition of this reagent is successful, providing the alcohol 3g in an acceptable 74% ee and 86% yield (Table 2, entry 8).
5.3 Mechanistic considerations

The working hypothesis of the mechanism of the reaction is presented in Figure 1. We surmise that upon reaction of the Grignard reagent with the chiral copper bromide complex, a new transmetallated species is formed, in which the alkyl moiety is more reactive than in the corresponding Grignard reagent. Furthermore, this species is capable of double activation of the substrate via a pseudo-chair transition state: Lewis acid activation of the carbonyl moiety through the Mg and activation of the carbonyl double bond by copper in analogy with the coordination mode of organocopper species reported recently by Bertz et al.37

![Figure 1: Proposed transition state for the reaction](image)

5.4 Summary and concluding remarks

In this chapter we report the first copper-catalyzed enantioselective 1,2-addition of Grignard reagents to aromatic ketones to deliver tertiary alcohols. A wide variety of commercially available aromatic ketones and Grignard reagents can be employed in this asymmetric addition with isolated yields up to 97% and enantioselectivities up to 98% ee. Furthermore, the optimal chiral ligand is commercially available, rendering this process an experimentally simple and practical method for construction of a variety of chiral benzylic tertiary alcohols. Finally, further study is needed to expand the scope of the reaction to the use of linear Grignard reagents and to its mechanism, especially the cause of enantioselectivity.

5.5 Experimental section

General

Flash chromatography: Merck silica gel type 9385 230-400 mesh, TLC: Merck silica gel 60, 0.25 mm. Components were visualized by UV and Seebach's reagent, a mixture of phosphomolybdic acid (25 g), cerium (IV) sulfate (7.5 g), H₂O (500 mL) and H₂SO₄ (25 mL) or potassium permanganate staining. Progress and conversion
of the reaction were determined by GC-MS (GC, HP6890: MS HP5973) with an HP1 or HP5 column (Agilent Technologies, Palo Alto, CA). High resolution mass spectra (HRMS) were recorded on a AEI-MS-902 and FTMS orbitrap (Thermo Fisher Scientific) mass spectrometer. $^1$H- and $^{13}$C-NMR were recorded on a Varian AMX400 (400 and 100.59 MHz, respectively) or a Varian Gemini 200, using CDCl$_3$ as solvent. Chemical shift values are reported in ppm with the solvent resonance as the internal standard (CHCl$_3$: $\delta$ 7.26 for $^1$H, $\delta$ 77.0 for $^{13}$C). Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz), and integration. Carbon assignments are based on APT $^{13}$C-NMR experiments. Optical rotations were measured on a Schimadzu LC-10AD VP HPLC equipped with a Schimadzu SPD-M10A VP diode array detector or by capillary GC analysis (HP 6890, CP-Chiralsil-Dex-CB column (25 m x 0.25 mm) or Chiraldex B-PM (30 m x 0.25 mm x 0.25 $\mu$m)) using a flame ionization detector.

All reactions were carried out under a nitrogen atmosphere using oven dried glassware and using standard Schlenk techniques. tBuOMe and dichloromethane were dried and distilled from calcium hydride; toluene, THF and n-hexane were dried and distilled from sodium. All copper salts were purchased from Aldrich, and used without further purification. All Star ting materials and Grignard reagents were purchased from Aldrich (iBuMgBr (2 M in Et$_2$O), EtMgBr (3 M in Et$_2$O), n-pentylMgBr (2 M in Et$_2$O)). Ligand ($S$,RFe)$\text{L}_1$ was purchased from Aldrich. Racemic products were synthesized by reaction of the ketones (1) and the corresponding Grignard reagents at rt in Et$_2$O. All Grignard reagents, when not commercial, were prepared from the corresponding alkyl bromides and Mg activated with $I_2$ in Et$_2$O.

General procedures for the copper-catalyzed 1,2-addition of Grignard reagents. 

Procedure A. addition to aromatic ketones 

A Schlenk tube equipped with septum and stirring bar was charged with CuBr•SMe$_2$ (0.015 mmol, 3.08 mg, 5 mol%) and ligand ($S,R_1$) $\text{L}_1$ (0.016 mmol, 6 mol%). Dry iBuOMe (3 mL) was added and the solution was stirred under nitrogen at room temperature for 15 min. Then, the corresponding ketone (0.3 mmol in 1 mL iBuOMe) was added and the resulting solution was cooled to −78 °C. The corresponding Grignard reagent (0.36 mmol, 1.2 eq, in Et$_2$O) was diluted with iBuOMe (combined volume of 1 mL) under nitrogen and added to the reaction mixture over 15 min. Once the addition was complete, the reaction mixture was monitored by TLC and GCMS. The reaction was quenched by the addition of MeOH (1 mL) and saturated aqueous NH$_4$Cl (2 mL) and the mixture was warmed to room temperature, diluted with Et$_2$O and the layers were separated. The aqueous layer was extracted with Et$_2$O (3 x 5 mL) and the combined organic layers were dried with anhydrous Na$_2$SO$_4$, filtered and the solvent was evaporated in
Asymmetric 1,2-addition of Grignard reagents to aromatic ketones

vacuo. The crude product was purified by flash chromatography on silica gel using mixtures of n-pentane and EtO as the eluent.

**Note:** Gas chromatography analysis was carried out to determine the 1,2-addition, 1,4-addition and 1,2-reduction ratio on a sample obtained after aqueous workup and extraction with EtO, which was passed through a short plug of silica gel to remove copper residues.

**Procedure B: addition to aromatic ketones**

A Schlenk tube equipped with septum and stirring bar was charged with CuBr·SMe₂ (0.015 mmol, 3.08 mg, 5 mol%) and ligand (S,R) L1 (0.018 mmol, 6 mol%). Dry tBuOMe (3 mL) was added and the solution was stirred under nitrogen at room temperature for 15 min. Then, the corresponding ketone (0.3 mmol in 1 mL tBuOMe) was added and the resulting solution was cooled to –60°C. The corresponding Grignard reagent (0.36 mmol, 1.2 eq, in tBuOMe) was diluted with tBuOMe (combined volume of 1 mL) under nitrogen and added to the reaction mixture over 15 min. Once the addition was complete, the reaction mixture was monitored by TLC and GCMS. The reaction was quenched by the addition of MeOH (1 mL) and saturated aqueous NH₄Cl (2 mL) and the mixture was warmed to room temperature, diluted with EtO and the layers were separated. The aqueous layer was extracted with EtO (3 x 5 mL) and the combined organic layers were dried with anhydrous Na₂SO₄, filtered and the solvent was evaporated in vacuo. The crude product was purified by flash chromatography on silica gel using mixtures of n-pentane and EtO as the eluent.

**Assignment of absolute configurations:**

The absolute configuration of all products was assigned by comparing the sign of the optical rotation to that of (R)-2-phenylbutan-2-ol (prepared by using the presented 1,2-addition reaction) with known absolute configuration.

(+)-(R)-4-Ethyl-2-phenylhexan-2-ol (2a)

Using method A: Reaction was performed with ligand (S,R) L1 and (2-ethylbutyl)magnesium bromide. Product 2a was obtained as a colorless oil after column chromatography (SiO₂, n-pentane:EtO 90:10), [96% yield, 82% ee]. ¹H NMR (400 MHz, CDCl₃) δ 7.44 (dd, J = 8.4, 1.2, 2H), 7.33 (dd, J = 10.4, 4.9, 2H), 7.25 – 7.18 (m, 1H), 1.72 (m, 2H), 1.62 (s, 1H), 1.56 (s, 3H), 1.26 – 1.11 (m, 5H), 0.74 (m, 6H). ¹³C NMR (101 MHz, CDCl₃) δ 127.98, 126.39, 124.83, 123.98, 126.39, 124.83, 75.20, 47.53, 36.17, 30.74, 26.67, 10.59. [α]D²⁰ = +12.0 (c = 0.3, CHCl₃). HRMS (ESI+, m/z): calcd for C₁₄H₂₂O·H [M–H]⁺: 189.1644; found: 189.1638. Enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel OJ column, n-heptane/i-PrOH 98:2, 145.
40 °C, detection at 240 nm, retention times (min): 5.3 (major) and 6.0 (minor). The absolute configuration of this compound is assumed to be (R), analogous to the other products.

\((\pm)-(R)-4\text{-ethyl-2-(p-tolyl)hexan-2-ol (2b)}\)

Using method B: Reaction was performed with ligand (S,R,R) Fe L1 and (2-ethylbutyl)magnesium bromide. Product 2b was obtained as a colorless oil after column chromatography (SiO₂, n-pentane/Et₂O 90:10), [85% yield, 76% ee].

\(^1\)H NMR (201 MHz, CDCl₃) δ 7.25 (d, \(J = 8.2\) Hz, 2H), 7.06 (d, \(J = 8.3\) Hz, 2H), 2.26 (s, 3H), 1.69 – 1.58 (m, 2H), 1.52 (s, 1H), 1.48 (s, 3H), 1.34 – 0.96 (m, 5H), 0.81 – 0.56 (m, 6H).

\(^{13}\)C NMR (50 MHz, CDCl₃) δ 145.55, 135.85, 128.73, 124.78, 75.23, 47.46, 36.18, 30.73, 26.50, 23.92, 10.58. \([\Delta]_D^{20} = +8 (c = 0.8, \text{CHCl}_3)\). HRMS (ESI+, \(m/z\)): calcd for C₁₅H₂₄O+Na [M+Na]⁺: 243.1719; found: 243.1719.

Enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel AD-H column, n-heptane/i-PrOH 99:1, 40 °C, detection at 240 nm, retention times (min): 15.2 (major) and 16.9 (minor).

\[(\pm)-(R)-4\text{-ethyl-2-(4-(trifluoromethyl)phenyl)hexan-2-ol (2c)}\]

Using method A: Reaction was performed with ligand (S,R,R) Fe L1 and (2-ethylbutyl)magnesium bromide. Product 2c was obtained as a colorless oil after column chromatography (SiO₂, n-pentane/Et₂O 90:10), [93% yield, 76% ee].

\(^1\)H NMR (201 MHz, CDCl₃) δ 7.60 (d, \(J = 9.4\) Hz, 4H), 1.74 (m, 2H), 1.70 (s, 1H), 1.57 (s, 3H), 1.39 – 1.53 (m, 5H), 0.74 (m, 6H). \(^{13}\)C NMR (50 MHz, CDCl₃) δ 152.40, 128.34, 125.37, 124.89, 121.57, 75.26, 47.38, 36.13, 31.00, 26.45, 10.44. \([\Delta]_D^{20} = +9.2 (c = 1.2, \text{CHCl}_3)\). HRMS (ESI+, \(m/z\)): calcd for C₁₅H₂₁F₃O–OH [M–OH]⁻: 257.1511; found: 257.1511.

Enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel AD-H column, n-heptane/i-PrOH 99:1, 40 °C, detection at 240 nm, retention times (min): 16.7 (major) and 20.3 (minor).
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(+)-(R)-4-ethyl-2-(4-fluorophenyl)hexan-2-ol (2d)

Using method A: Reaction was performed with ligand \((S,R)\) L1 and \((2\text{-ethylbutyl})\text{magnesium bromide}. Product 2d was obtained as a colorless oil after column chromatography (SiO\(_2\), n-pentane:Et\(_2\)O 90:10), [95% yield, 76% ee]. \(^1\)H NMR (201 MHz, CDCl\(_3\)): \(\delta 7.41 – 7.26 (m, 2H), 7.01 – 6.84 (m, 2H), 1.63 (m, 2H), 1.54 (s, 1H), 1.48 (s, 3H), 1.28 – 0.96 (m, 5H), 0.76 – 0.55 (m, 6H). \(^1^3\)C NMR (50 MHz, CDCl\(_3\)): \(\delta 163.92, 159.07, 126.55, 114.84, 75.00, 47.67, 36.24, 30.82, 26.65, 10.48\). \([\delta_{D20} = +7.9 (c = 1.2, \text{CHCl}_3)]\). HRMS (ESI+, \(m/z\)): calcd for C\(_{14}\)H\(_{21}\)FO–OH [M–OH]$: 207.1543; found: 207.1543. Enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel AD-H column, n-heptane/i-PrOH 99:1, 40 °C, detection at 240 nm, retention times (min): 19.4 (major) and 21.5 (minor).

(+)-(R)-2-(4-bromophenyl)-4-ethylhexan-2-ol (2e)

Using method B: Reaction was performed with ligand \((S,R)\) L1 and \((2\text{-ethylbutyl})\text{magnesium bromide}. Product 2e was obtained as a colorless oil after column chromatography (SiO\(_2\), n-pentane:Et\(_2\)O 90:10), [91% yield, 86% ee]. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 7.44 (d, J = 8.4, 2H), 7.31 (d, J = 8.5, 2H), 1.76 – 1.63 (m, 2H), 1.61 (s, 1H), 1.53 (s, 3H), 1.34 – 1.06 (m, 5H), 0.77 (t, J = 7.2, 3H), 0.70 (t, J = 7.3, 3H). \(^1^3\)C NMR (101 MHz, CDCl\(_3\)): \(\delta 147.42, 131.01, 126.82, 120.28, 75.02, 47.43, 36.23, 30.95, 26.61, 10.57\). \([\delta_{D20} = +8.2 (c = 1.4, \text{CHCl}_3)]\). HRMS (ESI+, \(m/z\)): calcd for C\(_{14}\)H\(_{21}\)BrO–OH [M–OH]$: 267.0742; found: 267.0742. Enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel AD-H column, n-heptane/i-PrOH 99:1, 40 °C, detection at 240 nm, retention times (min): 21.4 (major) and 25.2 (minor).

(+)-(R)-2-(3-chlorophenyl)-4-ethylhexan-2-ol (2f)

Using method A: Reaction was performed with ligand \((S,R)\) L1 and \((2\text{-ethylbutyl})\text{magnesium bromide}. Product 2f was obtained as a colorless oil after column chromatography (SiO\(_2\), n-pentane:Et\(_2\)O 90:10), [97% yield, 84% ee]. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 7.46 (t, J = 1.7, 1H), 7.35 – 7.15 (m, 3H), 1.71 (m, 2H),
1.68 (s, 1H), 1.54 (s, 3H), 1.33 – 1.07 (m, 5H), 0.78 (t, J = 7.2, 3H), 0.74 (m, J = 7.4, 3H). \(^1\)C NMR (101 MHz, CDCl\(_3\)) δ 150.72, 134.07, 129.27, 126.52, 125.28, 123.15, 75.09, 47.39, 36.11, 30.84, 26.56, 10.64. [\(d_{\text{D}20}\] = +13.9 (c = 1.5, CHCl\(_3\)).

HRMS (ESI\(^+\), m/z): calcd for C\(_{14}\)H\(_{21}\)ClO–OH \[M–OH\]⁺: 223.12480; found: 223.12479. Enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel AD-H column, n-heptane/i-PrOH 99:1, 40 °C, detection at 240 nm, retention times (min): 17.8 (major) and 19.1 (minor).

\((+)-(R)-2-(3-bromophenyl)-4-ethylhexan-2-ol (2g)\)

Using method B: Reaction was performed with ligand (S, R\(_8\)) L\(_1\) and (2-ethylbutyl)magnesium bromide. Product 2g was obtained as a colorless oil after column chromatography (SiO\(_2\), n-pentane:Et\(_2\)O 90:10), [96% yield, 90% ee]. \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 7.62 (t, J = 1.7, 1H), 7.40 – 7.31 (m, 2H), 7.19 (t, J = 7.9, 1H), 1.72 (s, 1H), 1.71 – 1.63 (m, 2H), 1.54 (s, 3H), 1.36 – 1.08 (m, 5H), 0.78 (t, J = 7.1, 3H), 0.71 (t, J = 7.4, 3H). \(^1\)C NMR (101 MHz, CDCl\(_3\)) δ 151.06, 129.46, 128.34, 123.62, 122.39, 74.91, 47.41, 36.22, 30.88, 26.78, 10.63. [\(d_{\text{D}20}\] = +11.8 (c = 2.2, CHCl\(_3\)). HRMS (ESI\(^+\), m/z): calcd for C\(_{14}\)H\(_{21}\)BrO–OH \[M–OH\]⁺: 267.07429; found: 267.07427. Enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel AD-H column, n-heptane/i-PrOH 99:1, 40 °C, detection at 240 nm, retention times (min): 18.0 (major) and 19.3 (minor).

\((+)-(R)-4-ethyl-2-(3-methoxyphenyl)hexan-2-ol (2h)\)

Using method B: Reaction was performed with ligand (S, R\(_8\)) L\(_1\) and (2-ethylbutyl)magnesium bromide. Product 2h was obtained as a colorless oil after column chromatography (SiO\(_2\), n-pentane:Et\(_2\)O 90:10), [87% yield, 54% ee]. \(^1\)H NMR (400 MHz, CDCl\(_3\)) δ 7.24 (t, J = 7.7, 1H), 7.07 – 6.96 (m, 2H), 6.81 – 6.72 (m, 1H), 3.82 (d, J = 0.8, 3H), 1.79 – 1.69 (m, 2H), 1.68 (s, 1H), 1.55 (s, 3H), 1.35 – 1.05 (m, 5H), 0.77 (t, J = 7.2, 3H), 0.72 (t, J = 7.4, 3H). \(^1\)C NMR (101 MHz, CDCl\(_3\)) δ 159.46, 150.32, 128.98, 117.37, 111.47, 111.01, 75.21, 55.18, 47.40, 36.24, 30.80, 26.56, 10.61. [\(d_{\text{D}20}\] = +7.6 (c = 1.1, CHCl\(_3\)). HRMS (ESI\(^+\), m/z): calcd for C\(_{15}\)H\(_{24}\)O\(_2\)–OH \[M–OH\]⁺: 219.17434; found: 219.17434. Enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel AD-H column, n-heptane/i-PrOH
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99:1, 40 °C, detection at 240 nm, retention times (min): 33 (minor) and 37.4 (major).

\((+)-(R)-4\)-ethyl-2-(3-(trifluoromethyl)phenyl)hexan-2-ol (2i)

\[
\text{Me} \quad \text{HO} \quad \text{Et} \quad \text{Et} \quad \text{CF}_3
\]

Using method A: Reaction was performed with ligand \((S, R)\) \(L_1\) and \((2\text{-ethylbutyl})\)magnesium bromide. Product 2i was obtained as a colorless oil after column chromatography (SiO\(_2\), n-pentane:Et\(_2\)O 90:10), [95\% yield, 96\% ee]. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.72 (s, 1H), 7.62 (d, \(J = 7.8\), 1H), 7.46 (m, 2H), 1.81 – 1.70 (m, 2H), 1.67 (s, 1H), 1.58 (s, 3H), 1.35 – 1.06 (m, 5H), 0.77 (t, \(J = 7.2\), 3H), 0.69 (t, \(J = 7.4\), 3H). \(^13\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 149.40, 128.50, 127.56, 123.35, 121.70, 75.06, 47.50, 36.12, 31.03, 26.23, 10.44. \([\delta]_D^{20} = +5.5 (c = 1, \text{CHCl}_3)\).

HRMS (ESI+, \(m/z\)): calcd for C\(_{15}\)H\(_{21}\)F\(_3\)O–OH (M–OH): 257.15116; found: 257.15116. Enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel AD-H column, n-heptane/i-PrOH 99:1, 40 °C, detection at 240 nm, retention times (min): 14.1 (major) and 14.7 (minor).

\((+)-(R)-4\)-ethyl-2-(m-tolyl)hexan-2-ol (6j)

\[
\text{Me} \quad \text{HO} \quad \text{Et} \quad \text{Et} \quad \text{Me}
\]

Using method B: Reaction was performed with ligand \((S, R)\) \(L_1\) and \((2\text{-ethylbutyl})\)magnesium bromide. Product 6j was obtained as a colorless oil after column chromatography (SiO\(_2\), n-pentane:Et\(_2\)O 90:10), [90\% yield, 76\% ee]. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.28 (s, 1H), 7.23 (m, 2H), 7.08 – 7.01 (m, 1H), 2.37 (s, 3H), 1.79 – 1.69 (m, 2H), 1.66 (s, 1H), 1.56 (s, 3H), 1.37 – 1.06 (m, 5H), 0.79 (t, \(J = 7.2\), 3H), 0.73 (t, \(J = 7.4\), 3H). \(^13\)C NMR (101 MHz, CDCl\(_3\)) \(\delta\) 148.54, 137.50, 127.89, 127.11, 125.54, 121.89, 127.89, 127.11, 125.54, 121.89, 75.19, 47.61, 36.18, 30.68, 26.61, 21.64, 10.64. \([\delta]_D^{20} = +9.4 (c = 1.7, \text{CHCl}_3)\).

HRMS (ESI+, \(m/z\)): calcd for C\(_{15}\)H\(_{24}\)O\(_2\)+Na (M+Na): 243.17194; found: 243.17194. Enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel AD-H column, n-heptane/i-PrOH 99:1, 40 °C, detection at 240 nm, retention times (min): 16.4 (major) and 17.2 (minor).
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(+)-(R)-5-ethyl-3-(3-(trifluoromethyl)phenyl)heptan-3-ol (2k)

Using method A: Reaction was performed with ligand \((S, R_e) L_1\) and (2-ethylbutyl)magnesium bromide. Product 2k was obtained as a colorless oil after column chromatography (SiO\(_2\), n-pentane:Et\(_2\)O 90:10), [97% yield, 84% ee]. \(^1\)H NMR (201 MHz, CDCl\(_3\)) \(\delta 7.60 (s, 1H), 7.41 (m, 3H), 1.93 – 1.61 (m, 4H), 1.54 (s, 1H), 1.36 – 0.86 (m, 5H), 0.79 – 0.49 (m, 9H).\)

13C NMR (50 MHz, CDCl\(_3\)) \(\delta 147.35, 128.91, 128.29, 123.08, 77.49, 46.32, 36.08, 35.60, 26.42, 10.53, 7.53\). [\(\delta_d\) = +6 (c = 2, CHCl\(_3\)). HRMS (ESI+, m/z): calcd for C\(_{15}\)H\(_{21}\)F\(_3\)O–OH [M–OH]\(^+\): 257.15116; found: 257.15115. Enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel AD-H column, n-heptane/i-PrOH 99:1, 40 °C, detection at 240 nm, retention times (min): 10.8 (minor) and 15.3 (major).

(+)-4-ethyl-2-(2-fluorophenyl)hexan-2-ol (2l)

Using method B: Reaction was performed with ligand \((S, R_e) L_1\) and (2-ethylbutyl)magnesium bromide. Product 2l was obtained as a colorless oil after column chromatography (SiO\(_2\), n-pentane:Et\(_2\)O 90:10), [84% yield, 70% ee]. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 7.56 (t, J = 8.1, 1H), 7.24 – 7.18 (m, 1H), 7.12 (t, J = 7.5, 1H), 6.99 (dd, J = 12.2, 8.1, 1H), 2.06 – 1.68 (m, 2H), 1.62 (s, 3H), 1.57 (s, 1H), 1.38 – 1.05 (m, 5H), 0.77 (t, J = 7.3, 3H), 0.69 (t, J = 7.3, 3H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta 158.66, 134.78, 128.87, 127.11, 123.80, 115.81, 74.04, 45.08, 36.37, 29.69, 26.38, 10.48.\) [\(\delta_d\) = +6 (c = 0.75, CHCl\(_3\)). HRMS (ESI+, m/z): calcd for C\(_{14}\)H\(_{21}\)FO–OH [M–OH]\(^+\): 207.15435; found: 207.15435. Enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel AD-H column, n-heptane/i-PrOH 99:1, 40 °C, detection at 240 nm, retention times (min): 16.0 (major) and 17.4 (minor).

(+)-(R)-2-(2-bromophenyl)-4-methylpentan-2-ol (2m)

Using method A: Reaction was performed with ligand \((S, R_e) L_1\) and iBuMgBr. Product 2m was obtained as a colorless oil after column chromatography (SiO\(_2\), n-pentane:Et\(_2\)O 90:10), [81% yield, 95% ee]. \(^1\)H NMR (201 MHz, CDCl\(_3\)) \(\delta 8.1 (s, 1H), 7.41 – 7.31 (m, 2H), 7.19 (s, 1H), 7.15 (m, 3H), 1.93 – 1.61 (m, 4H), 1.54 (s, 1H), 1.36 – 0.86 (m, 5H), 0.79 – 0.49 (m, 9H).\)

13C NMR (50 MHz, CDCl\(_3\)) \(\delta 158.66, 134.78, 128.87, 127.11, 123.80, 115.81, 74.04, 45.08, 36.37, 29.69, 26.38, 10.48.\) [\(\delta_d\) = +6 (c = 2, CHCl\(_3\)). HRMS (ESI+, m/z): calcd for C\(_{15}\)H\(_{21}\)BrO–OH [M–OH]\(^+\): 277.15115; found: 277.15116. Enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel AD-H column, n-heptane/i-PrOH 99:1, 40 °C, detection at 240 nm, retention times (min): 15.5 (minor) and 20.1 (major).
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7.71 (dd, \(J = 7.9, 1.8\), 1H), 7.49 (dd, \(J = 7.8, 1.3\), 1H), 7.32 – 7.15 (m, 1H), 7.01 (m, 1H), 2.35 (m, 2H), 2.17 (s, 1H), 1.65 (s, 3H), 1.48 (m, 1H), 0.78 (d, \(J = 6.6\), 3H), 0.73 (d, \(J = 6.6\), 3H). \(^{13}C\) NMR (50 MHz, CDCl\(_3\)) δ 145.57, 134.87, 128.11, 127.35, 120.39, 76.26, 49.07, 29.07, 24.79, 24.07, \([\delta_p]^{25}_{D} = +3.6\) (c = 1.1, CHCl\(_3\)).

Enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel OJ-H column, n-heptane/i-PrOH 99:1, 40 °C, detection at 240 nm, retention times (min): 35.7 (major) and 37.4 (minor).

(+)-(R)-2-(3,4-dichlorophenyl)-4-ethylhexan-2-ol (2n)

Using method A: Reaction was performed with ligand (S, R\(_{R}\)) \(\text{L}_1\) and (2-ethylbutyl)magnesium bromide. Product 2n was obtained as a colorless oil after column chromatography (SiO\(_2\), n-pentane:Et\(_2\)O 90:10). [96% yield, 96% ee].

\(^1H\) NMR (400 MHz, CDCl\(_3\)) δ 7.55 (d, \(J = 2.1\), 1H), 7.38 (d, \(J = 8.4\), 1H), 7.24 (dd, \(J = 8.4, 2.1\), 1H), 1.68 (s, 1H), 1.67 (m, 2H), 1.53 (s, 3H), 1.36 – 1.04 (m, 5H), 0.78 (t, \(J = 7.2\), 3H), 0.71 (t, \(J = 7.3\), 3H). \(^{13}C\) NMR (101 MHz, CDCl\(_3\)) δ 148.83, 132.10, 130.26, 129.90, 127.25, 124.56, 74.80, 47.28, 36.11, 30.94, 26.46, 10.58, \([\delta_p]^{25}_{D} = +12.54\) (c = 1.7, CHCl\(_3\)).

HRMS (ESI\(^+\), m/z): calcd for C\(_{14}\)H\(_{20}\)Cl\(_2\)ONa [M+Na\(^+\)]: 297.07834; found: 297.07833. Enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel AD-H column, n-heptane/i-PrOH 99:1, 40 °C, detection at 240 nm, retention times (min): 16.5 (major) and 17.1 (minor).

(+)-(R)-2-(3,5-difluorophenyl)-4-ethylhexan-2-ol (2o)

Using method A: Reaction was performed with ligand (S, R\(_{R}\)) \(\text{L}_1\) and (2-ethylbutyl)magnesium bromide. Product 2o was obtained as a colorless oil after column chromatography (SiO\(_2\), n-pentane:Et\(_2\)O 90:10). [96% yield, 92% ee].

\(^1H\) NMR (400 MHz, CDCl\(_3\)) δ 7.02 – 6.89 (m, 2H), 6.66 (m, 1H), 1.74 – 1.68 (m, 2H), 1.67 (s, 1H), 1.53 (s, 3H), 1.35 – 1.06 (m, 5H), 0.79 (t, \(J = 7.2\), 3H), 0.71 (t, \(J = 7.3\), 3H). \(^{13}C\) NMR (101 MHz, CDCl\(_3\)) δ 164.09, 161.57, 152.83, 108.20, 101.70, 75.02, 47.24, 36.08, 30.79, 26.51, 10.44, \([\delta_p]^{25}_{D} = +12.1\) (c = 1.2, CHCl\(_3\)).

HRMS (ESI\(^+\), m/z): calcd for C\(_{14}\)H\(_{20}\)F\(_2\)O–OH [M–OH\(^+\)]: 225.14493; found: 225.14493. Enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel AD-H column, n-heptane/i-PrOH 99:1, 40 °C, detection at 240 nm, retention times (min): 16.5 (major) and 17.1 (minor).
(+)-(R)-2-(3,5-bis(trifluoromethyl)phenyl)-4-ethylhexan-2-ol (2p)

Using method A: Reaction was performed with ligand (S, R) FeL₁ and (2-ethylbutyl)magnesium bromide. Product 2p was obtained as a colorless oil after column chromatography (SiO₂, n-pentane:Et₂O 90:10), [95% yield, 98% ee].

1H NMR (400 MHz, CDCl₃) δ 7.91 (s, 2H), 7.76 (s, 1H), 1.77 (m, 2H), 1.61 (s, 3H), 1.35 – 1.04 (m, 5H), 0.79 (t, J = 7.3, 3H), 0.68 (t, J = 7.3, 3H). 13C NMR (101 MHz, CDCl₃) δ 151.05, 131.43, 131.10, 125.36, 120.46, 74.97, 47.33, 36.22, 31.02, 26.80, 26.47, 10.58, 10.39. [δ]D₂₀ = +9.1 (c = 1.5, CHCl₃). HRMS (ESI+, m/z): calcd for C₁₆H₂₀F₆O–OH [M–OH]+: 325.13854; found: 325.13851. Enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel AS-H column, n-heptane/i-PrOH 99:1, 40 °C, detection at 240 nm, retention times (min): 7.3 (major) and 7.9 (minor).

(+)-(R)-4-ethyl-2-(naphthalen-2-yl)hexan-2-ol (2q)

Using method B: Reaction was performed with ligand (S, R) FeL₁ and (2-ethylbutyl)magnesium bromide. Product 2q was obtained as a colorless oil after column chromatography (SiO₂, n-pentane:Et₂O 90:10), [91% yield, 66% ee].

1H NMR (400 MHz, CDCl₃) δ 7.91 (s, 1H), 7.91 – 7.80 (m, 3H), 7.59 – 7.44 (m, 3H), 1.95 – 1.79 (m, 2H), 1.68 (s, 3H), 1.42 – 1.11 (m, 5H), 0.81 (t, J = 7.1, 3H), 0.74 (t, J = 7.4, 3H). 13C NMR (101 MHz, CDCl₃) δ 145.82, 133.19, 133.19, 132.20, 128.17, 127.69, 127.42, 126.02, 125.55, 123.98, 123.08, 75.46, 47.20, 36.21, 31.04, 26.50, 10.68. [δ]D₂₀ = +10.4 (c = 2.2, CHCl₃). HRMS (ESI+, m/z): calcd for C₁₈H₂₄O+Na [M+Na]+: 279.17194; found: 279.17194. Enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel AD-H column, n-heptane/i-PrOH 99:1, 40 °C, detection at 240 nm, retention times (min): 23.4 (major) and 24.7 (minor).

(−)-(S)-4-ethyl-2-(naphthalen-1-yl)hexan-2-ol (2r)

Using method A: Reaction was performed with ligand (S, R) FeL₁ and (2-ethylbutyl)magnesium bromide. Product 2r was obtained as a colorless oil after column chromatography (SiO₂, n-pentane:Et₂O 90:10), [71% yield, 95% ee].
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NMR (400 MHz, CDCl₃): δ 8.72 (d, J = 8.3, 1H), 7.93 – 7.83 (m, 1H), 7.77 (d, J = 8.1, 1H), 7.64 (d, J = 7.3, 1H), 7.55 – 7.38 (m, 3H), 2.14 (m, 2H), 1.98 (s, 1H), 1.85 (s, 3H), 1.33 – 1.03 (m, 5H), 0.77 (t, J = 7.1, 3H), 0.62 (s, J = 7.4, 3H). ¹³C NMR (101 MHz, CDCl₃): δ 143.17, 134.80, 130.99, 129.15, 129.12, 126.90, 125.02, 124.79, 123.59, 76.84, 45.77, 36.97, 30.57, 26.77, 10.67. [D₂O]: δ = –17.8 (c = 1.4, CHCl₃). HRMS (ESI+, m/z): calcd for C₁₈H₂₄ONa [M+Na]⁺: 279.17194; found: 279.17194. Enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel AD-H column, n-heptane/i-PrOH 99:1, 40 °C, detection at 240 nm, retention times (min): 22.6 (major) and 24.8 (minor).

(+)-(R)-2-(anthracen-2-yl)-4-ethylhexan-2-ol (2s)

Using method B: Reaction was performed with ligand (S,R)-FeL₁ and (2-ethylbutyl)magnesium bromide. Product 2s was obtained as a light yellow solid after column chromatography (SiO₂, n-pentane:Et₂O 90:10), [88% yield, 80% ee]. ¹H NMR (400 MHz, CDCl₃): δ 8.50 (dd, J = 72.6, 20.8, 2H), 8.13 – 7.92 (m, 4H), 7.61 – 7.41 (m, 3H), 2.75 (s, 1H), 1.89 (m, 2H), 1.70 (s, 3H), 1.41 – 1.08 (m, 5H), 0.79 (t, J = 7.2, 3H), 0.71 (t, J = 7.4, 3H). ¹³C NMR (101 MHz, CDCl₃): δ 144.99, 131.85, 131.61, 131.43, 130.63, 128.94, 129.71, 128.62, 128.14, 127.89, 126.68, 126.37, 125.76, 125.28, 124.11, 122.75, 75.47, 46.85, 36.31, 30.66, 26.68, 10.63. [D₂O]: δ = +3.6 (c = 1.7, CHCl₃). HRMS (ESI+, m/z): calcd for C₂₂H₂₆O–OH [M–OH]⁺: 289.19508; found: 289.19508. Enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel AD-H column, n-heptane/i-PrOH 99:1, 40 °C, detection at 240 nm, retention times (min): 38.2 (minor) and 44.1 (major).

(+)-(R)-4-ethyl-2-(thiophen-3-yl)hexan-2-ol (2t)

Using method A: Reaction was performed with ligand (S,R)-FeL₁ and (2-ethylbutyl)magnesium bromide. Product 2t was obtained as a colorless oil after column chromatography (SiO₂, n-pentane:Et₂O 90:10), [96% yield, 76% ee]. ¹H NMR (400 MHz, CDCl₃): δ 7.25 (dd, J = 4.6, 3.2, 1H), 7.17 – 7.09 (m, 1H), 7.03 (d, J = 5.0, 1H), 1.77 (s, 1H), 1.69 (d, J = 5.1, 2H), 1.55 (s, 3H), 1.30 – 1.12 (m, 5H), 0.75 (m, 6H). ¹³C NMR (101 MHz, CDCl₃): δ 150.52, 125.88, 125.53, 119.14, 74.19, 47.28, 36.21, 30.18, 26.60, 10.64. [D₂O]: δ = +1.6 (c = 1.3, CHCl₃). HRMS (ESI+, m/z): calcd for C₁₂H₂₀O–OH [M–OH]⁺: 195.12020; found: 195.12019. Enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel AD-H column, n-heptane/i-PrOH 99:1, 40 °C, detection at 240 nm, retention times (min): 26.5 (minor) and 29.9 (major).
Chapter 5

(–)-(S)-2-(3,5-bis(trifluoromethyl)phenyl)butan-2-ol (3a)

Using method A. Reaction was performed with ligand (S, R)<sub>Fe</sub> L1 and EtMgBr. Product 3a was obtained as a colorless oil after column chromatography (SiO<sub>2</sub>, n-pentane:Et<sub>2</sub>O 90:10), [94% yield, 22% ee]. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.90 (s, 2H), 7.76 (s, 1H), 1.91 – 1.85 (m, 2H), 1.84 (bs, 1H), 1.59 (s, 3H), 0.86 – 0.78 (t, J = 7.3, 3H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 150.42, 131.52, 125.56, 124.77, 120.53, 74.68, 36.73, 29.79, 8.00. [δ<sub>D20</sub>] = −1.1 (c = 1.0, CHCl<sub>3</sub>). HRMS (ESI+, m/z): calcd for C<sub>12</sub>H<sub>12</sub>F<sub>6</sub>O–OH [M–OH]⁺: 269.07594; found: 269.07594. Enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel OD-H column, n-heptane/i-PrOH 99:1, 40 °C, detection at 240 nm, retention times (min): 17.0 (major) and 17.7 (minor).

(–)-(S)-2-(3,5-bis(trifluoromethyl)phenyl)hex-5-en-2-ol (3b)

Using method A. Reaction was performed with ligand (S, R)<sub>Fe</sub> L1 and but-3-en-1-ylmagnesium bromide. Product 3b was obtained as a colorless oil after column chromatography (SiO<sub>2</sub>, n-pentane:Et<sub>2</sub>O 97:3), [92% yield, 44% ee]. <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 7.90 (s, 2H), 7.77 (s, 1H), 5.88 – 5.70 (m, 1H), 4.97 (m, 2H), 2.01 (s, 1H), 1.99 – 1.85 (m, 4H), 1.61 (s, 3H). <sup>13</sup>C NMR (101 MHz, CDCl<sub>3</sub>) δ 150.43, 137.83, 131.30, 125.25, 122.07, 120.66, 115.34, 74.53, 42.88, 30.39, 28.22. [δ<sub>D20</sub>] = −1.6 (c = 1.4, CHCl<sub>3</sub>). HRMS (ESI+, m/z): calcd for C<sub>14</sub>H<sub>14</sub>F<sub>6</sub>O–OH [M–OH]⁺: 295.09159; found: 295.09159. Enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel OD-H column, n-heptane/i-PrOH 99:1, 40 °C, detection at 240 nm, retention times (min): 13.5 (major) and 14.1 (minor).
Asymmetric 1,2-addition of Grignard reagents to aromatic ketones

(-)-(S)-2-(3,5-bis(trifluoromethyl)phenyl)-4-phenylbutan-2-ol (3c)

Using method A: Reaction was performed with ligand \((S, R)\) FeL1 and phenethylmagnesium bromide. Product 3c was obtained as a colorless oil after column chromatography (SiO\(_2\), n-pentane:Et\(_2\)O 90:10), [93% yield, 68% ee]. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 7.95\) (s, 2H), 7.80 (s, 1H), 7.27 (t, \(J = 7.3\), 2H), 7.16 (t, \(J = 7.3\), 1H), 7.11 (d, \(J = 7.4\), 2H), 2.79 – 2.37 (m, 2H), 2.24 – 2.14 (m, 2H), 1.93 (s, 1H), 1.67 (s, 3H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta 150.34, 141.23, 131.75, 131.36, 128.54, 128.29, 128.06, 125.03, 120.79, 74.49, 45.77, 30.53, 30.19, [\(\alpha\)]\(_{D}\)\(= +2.7\) (c = 1.5, CHCl\(_3\)). HRMS (ESI+, \(m/z\)): calcd for C\(_{18}\)H\(_{16}\)F\(_6\)O–OH \([M–OH]^{+}\): 345.10724; found: 345.10722. Enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel OJ-H column, n-heptane/i-PrOH 99:1, 40 °C, detection at 240 nm, retention times (min): 19.4 (major) and 20.6 (minor).

(+)-(R)-2-(3,5-bis(trifluoromethyl)phenyl)-4-methylpentan-2-ol (3d)

Using method A: Reaction was performed with ligand \((S, R)\) L1 and iBuMgBr. Product 3d was obtained as a colorless oil after column chromatography (SiO\(_2\), n-pentane:Et\(_2\)O 90:10), [95% yield, 95% ee]. \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta 7.91\) (s, 2H), 7.76 (s, 1H), 1.83 (s, 1H), 1.81 (m, 2H), 1.74 (m, 1H), 1.60 (s, 3H), 0.92 (d, \(J = 6.6\), 3H), 0.75 (d, \(J = 6.6\), 3H). \(^{13}\)C NMR (101 MHz, CDCl\(_3\)) \(\delta 151.11, 131.49, 131.16, 125.26, 120.54, 75.02, 52.46, 31.55, 24.35, 23.47 [\(\alpha\)]\(_{D}\)\(= +4.6\) (c = 1.5, CHCl\(_3\)). HRMS (ESI+, \(m/z\)): calcd for C\(_{14}\)H\(_{16}\)F\(_6\)O–OH \([M–OH]^{+}\): 297.10724; found: 297.10723. Enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel AD-H column, n-heptane/i-PrOH 99:1, 40 °C, detection at 240 nm, retention times (min): 10.3 (minor) and 10.6 (major).
(+)-(R)-2-(3,5-bis(trifluoromethyl)phenyl)-4-ethyloctan-2-ol (3e)

Using method A: Reaction was performed with ligand (S, R)FeL1 and (2-ethylhexyl)magnesium bromide. Product 3e was obtained as a colorless oil after column chromatography (SiO2, n-pentane:Et2O 90:10), [91% yield, 1:1 dr, 98% ee]. 1H NMR (400 MHz, CDCl3) δ 7.91 (s, 2H), 7.76 (s, 1H), 1.81 – 1.74 (m, 3H), 1.61 (s, 3H), 1.36 – 0.92 (m, 9H), 0.90 – 0.64 (m, 8H). 13C NMR (101 MHz, CDCl3) δ 151.03, 131.43, 131.21, 125.42, 120.43, 120.43, 74.97, 47.83, 34.81, 34.20, 33.80, 31.27, 30.87, 28.68, 28.47, 27.36, 26.93, 22.90, 22.76, 13.97, 13.82, 10.55, 10.37. [α]D20 = +8.9 (c = 1.7, CHCl3). HRMS (ESI+, m/z): calcd for C18H24F6O–OH [M–OH]+: 353.16984; found: 353.16983. Enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel OJ-H column, n-heptane/i-PrOH 99:1, 40 °C, detection at 240 nm, retention times (min): 8.1 (minor) and 8.9 (major).

(+)-(R)-2-(3,5-bis(trifluoromethyl)phenyl)-1-cyclohexylpropan-2-ol (3f)

Using method A: Reaction was performed with ligand (S, R)FeL1 and (cyclohexylmethyl)magnesium bromide. Product 3f was obtained as a colorless oil after column chromatography (SiO2, n-pentane:Et2O 90:10), [97% yield, 98% ee]. 1H NMR (400 MHz, CDCl3) δ 7.91 (s, 2H), 7.76 (s, 1H), 1.76 (d, J = 5.5, 2H), 1.58 (s, 3H), 1.44 – 0.78 (m, 11H). 13C NMR (101 MHz, CDCl3) δ 151.17, 131.45, 131.12, 125.27, 122.11, 75.01, 51.34, 35.02, 34.73, 33.67, 31.26, 26.05. [α]D20 = +6.9 (c = 1.9, CHCl3). HRMS (ESI+, m/z): calcd for C17H20F6O–OH [M–OH]+: 337.13854; found: 337.13854. Enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel OJ-H column, n-heptane/i-PrOH 99:1, 40 °C, detection at 240 nm, retention times (min): 11.5 (minor) and 12.1 (major).

(+)-(R)-2-(3,5-bis(trifluoromethyl)phenyl)-1-(trimethylsilyl)propan-2-ol (3g)

Using method A: Reaction was performed with ligand (S, R)FeL1 and ((trimethylsilyl)methyl)magnesium bromide. Product 3g was obtained as a colorless oil after column chromatography (SiO2, n-pentane:Et2O 90:10), [97% yield, 98% ee]. 1H NMR (400 MHz, CDCl3) δ 7.91 (s, 2H), 7.76 (s, 1H), 1.76 (d, J = 5.5, 2H), 1.58 (s, 3H), 1.44 – 0.78 (m, 11H). 13C NMR (101 MHz, CDCl3) δ 151.17, 131.45, 131.12, 125.27, 122.11, 75.01, 51.34, 35.02, 34.73, 33.67, 31.26, 26.05. [α]D20 = +6.9 (c = 1.9, CHCl3). HRMS (ESI+, m/z): calcd for C18H24F6O–OH [M–OH]+: 353.16984; found: 353.16983. Enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel OJ-H column, n-heptane/i-PrOH 99:1, 40 °C, detection at 240 nm, retention times (min): 8.1 (minor) and 8.9 (major).
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colorless oil after column chromatography (SiO$_2$, n-pentane:EtO$_2$ 90:10), [86% yield, 74% ee]. $^1$H NMR (400 MHz, CDCl$_3$) $^\delta$ 7.94 (s, 2H), 7.75 (s, 1H), 1.84 (s, 1H), 1.66 (s, 3H), 1.39 (s, 2H), -0.11 (s, 9H). $^{13}$C NMR (101 MHz, CDCl$_3$) $^\delta$ 152.62, 131.47, 131.12, 125.05, 120.29, 74.80, 34.97, 33.98, -0.15. $\alpha$D$_{20}$ = +5.8 (c = 1.8, CHCl$_3$). HRMS (ESI+, m/z): calcd for C$_{14}$H$_{18}$F$_6$OSi–OH [M–OH]$^+$: 327.09982; found: 327.09982. Enantiomeric ratio was determined by chiral HPLC analysis, Chiralcel AD-H column, n-heptane/i-PrOH 99:1, 40 °C, detection at 240 nm, retention times (min): 8.5 (minor) and 8.9 (major).

5.6 References

(23) D. Tornita; M. Kanai; Shibasaki, M. Chem.-Asian J. 2006, 1, 161.
Chapter 5