Supporting Information

Catalytic enantioselective Reformatsky reaction with ketones

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Table of Contents

<table>
<thead>
<tr>
<th>General Information</th>
<th>S1</th>
</tr>
</thead>
<tbody>
<tr>
<td>General Procedure for the Enantioselective Reformatsky Reaction</td>
<td>S2</td>
</tr>
</tbody>
</table>

**General Information:** Chromatography: Merck silica gel type 9385 230-400 mesh, TLC: Merck silica gel 60, 0.25 mm. Visualization of the chromatograms was performed by UV and phosphomolibdic acid 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). Mass spectra were recorded on an AEI-MS-902 mass spectrometer. \(^{1}\)H- and \(^{13}\)C-NMR were recorded on a Varian AMX400 (400 and 100.59 MHz, respectively) 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, sep = septet, br = broad, m = multiplet), coupling constants (Hz), and integration. Optical rotations were measured on a Schmidt + Haensch polarimeter (Polartronic MH8) with a 10 cm cell (c given in g/100 mL). Absolute configurations were determined by comparison of the sign of the optical rotation with the literature values.

Enantioselectivities were determined by capillary GC analysis using a flame ionization detector (in comparison with racemic products). HPLC analysis was carried out on a Shimadzu LC-10AD VP HPLC equipped with a Shimadzu SPD-M10AVP diode array detector. Et\(_2\)O was dried with sodium/benzophenone and distilled. All ketones were purchased and used without further purification. Me\(_2\)Zn (2M in toluene) was purchased from Fluka. All racemic \(\beta\)-hydroxyesters were prepared by mixing the corresponding reagents and stirring for 1 h under air at room temperature. Ligands (S)-L1 and (S)-L4 are commercially available. Ligand (S)-L3 was synthesized following the procedure described in the literature.\(^1\)

Synthesis of (S)-3,3'-bis(trimethylsilyl)1,1'-binaphthyl-2,2'-diol [(S)-L2]

\[
\begin{align*}
\text{OMOM} & \quad \text{OMOM} \\
\text{i} & \quad \text{n-BuLi} & \quad \text{TMEDA} & \quad \text{Me}_3\text{SiCl} & \quad \text{Et}_2\text{O} \\
\text{TMS} & \quad \text{TMS} & \quad \text{HCl} & \quad \text{THF} & \quad \text{reflux} \\
\text{OH} & \quad \text{OH} & \quad \text{TMS} & \quad \text{OMOM} & \quad \text{OMOM} \\
\end{align*}
\]

Binol derivative i (2g, 5.34 mmol) was dissolved in Et\(_2\)O (100 mL) followed by addition at room temperature of TMEDA (4.32 mL, 28.05 mmol) and n-BuLi (14.71 mL, 1.6M, 23.55 mmol). The resulting suspension was stirred at 35 °C for 30 min. The mixture was cooled down to room temperature and chlorotrimethylsilane (4.53 mL, 34.90 mmol) was added followed by stirring for 16 h. The reaction was quenched by addition of sat. aq. NH\(_4\)Cl, then extracted with CH\(_2\)Cl\(_2\). The combined organic layers were dried over MgSO\(_4\), filtered and the solvent evaporated under reduced pressure to give a yellow oil. The product was purified by flash column chromatography (pentane:E\(_2\)O 45:1) to yield the product as a white solid. Aq. HCl (6M) (90 mL) was added to a solution of ii (5.34 mmol) in THF (90 mL). The resulting solution was heated at 60 °C for 21 h. The reaction mixture was cooled down to room temperature. The product was extracted with Et\(_2\)O and the organic phases were dried over MgSO\(_4\) before concentration.

MgSO₄, filtered and the solvent evaporated under reduced pressure. The product was purified by flash column chromatography (pentane) to give (S)-L2 as white solid in 85% yield (two steps).

\[ \alpha_\text{D} = -148 \text{ (c = 1.0, THF)} \text{, Lit.}^1 \ (R) \alpha_\text{D} = +143 \text{ (c = 0.98, THF)} . \]

\(^1\)H-NMR \( \delta \ 0.41 \text{ (s, 18H)}, 5.22 \text{ (s, 2H)}, 7.10 \text{ (d, } J = 8.2 \text{ Hz, 2H)}, 7.23-7.38 \text{ (m, 4H)}, 7.89 \text{ (d, } J = 7.9 \text{ Hz, 2H)}, 8.07 \text{ (s, 2H)} .

**General Procedure for the Enantioselective Reformatsky Reaction:** In a two necked 50 mL round bottom flask\(^2\) equipped with a CaCl₂ tube, Et₂O (5 mL), (S)-L2 (0.025 mmol, 20 mol%) and ethyl iodoacetate (0.5 mmol, 2 equiv) were added at room temperature. Me₂Zn (1 mmol, 4 equiv, 2M solution in toluene) was added and immediately the addition over a 30 min period of a solution of ketone (0.25 mmol) in Et₂O (1 mL) was started using a syringe pump.\(^3\) After 15 min, a new portion of Me₂Zn (1 mmol, 4 equiv, 2M solution in toluene) was added. The resulting solution was stirred for 1 h and quenched with aq. NH₄Cl. The organic phase was separated and the aqueous phase extracted with Et₂O (5 mL). The combined organic phases were dried over MgSO₄ and the solvent evaporated under reduced pressure to give the corresponding hydroxyester. The product was purified by flash chromatography.

(3R) Ethyl 3-hydroxy-3-phenylbutanoate (2a)

![Chemical structure of 2a](image1.png)

2a was obtained following the general procedure, after purification by flash chromatography (pentane:Et₂O 3:1), as a colorless oil (73% yield, 77% ee). Analytical data are in accordance with the lit.\(^4\)

\[ [\alpha_\text{D}] = -14 \text{ (c = 1.65, CHCl₃)} \text{, Lit.}^4 (R) [\alpha_\text{D}] = -8.69 \text{ (c = 0.46, EtOH)} , \text{ optical purity 66%.} \]

_Ee determination by chiral HPLC analysis, Chiralpak OJ-H column, Heptane:i-PrOH 99:1, retention times: 34.9 min (R), 48.2 min (S)._)

Ethyl (1-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)-acetate (2b)

![Chemical structure of 2b](image2.png)

2b was obtained following the general procedure, after purification by flash chromatography (pentane:Et₂O 3:1), as a colorless oil (65% yield, 90% ee). Analytical data are in accordance with the lit.\(^4\)

\[ [\alpha_\text{D}] = +20 \text{ (c = 1.3, CHCl₃)} . \]

_Ee determination by chiral HPLC analysis, Chiralpak AD column, Heptane:i-PrOH 95:5, retention times: 8.6 min (major), 10.9 min (minor)._)

(1R) Ethyl (1-hydroxy-2,3-dihydro-1H-inden-1-yl)acetate (2c)

![Chemical structure of 2c](image3.png)

2c was obtained following the general procedure, after purification by flash chromatography (pentane:Et₂O 3:1), as a colorless oil (64% yield, 80% ee). Analytical data are in accordance with the lit.\(^4\)

\[ [\alpha_\text{D}] = +5 \text{ (c = 0.8, CHCl₃)} \text{, Lit.}^4 (R) [\alpha_\text{D}] = +4.2 \text{ (c = 2.6, CHCl₃)} , \text{ optical purity 84%}. \]

_Ee determination by chiral HPLC analysis, Chiralcel OD column, Heptane:i-PrOH 95:5, retention times: 7.9 min (R), 9.6 min (S)._)

Ethyl 3-(4-chlorophenyl)-3-hydroxybutanoate (2d)

![Chemical structure of 2d](image4.png)

2d was obtained following the general procedure, after purification by flash chromatography (pentane:Et₂O 3:1), as a colorless oil (80% yield, 85% ee). Analytical data are in accordance with the lit.\(^4\)

\[ [\alpha_\text{D}] = -10 \text{ (c = 2.25, CHCl₃)} . \]

_Ee determination by chiral HPLC analysis, Chiralpack OD-H column, Heptane:i-PrOH 95:5, retention times: 10.8 min (major), 12.0 min (minor)._)

(3R) Ethyl 3-(4-bromophenyl)-3-hydroxybutanoate (2e)

![Chemical structure of 2e](image5.png)

2e was obtained following the general procedure, after purification by flash chromatography (pentane:Et₂O 3:1), as a colorless oil (85% yield, 74% ee). Analytical data are in accordance with the lit.\(^4\)

\[ [\alpha_\text{D}] = -11 \text{ (c = 2.25, CHCl₃)} \text{, Lit.}^4 (R) [\alpha_\text{D}] = -9.7 \text{ (c = 2, CHCl₃), optical purity 80%}. \]

_Ee determination by chiral HPLC analysis, Chiralpack OD-H column, Heptane:i-PrOH 95:5, retention times: 11.6 min (R), 12.7 min (S)._)

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\(^2\) It is necessary to use a relative large size flask in order to have a good contact between oxygen and dimethylzinc.

\(^3\) It is necessary to start the addition of ketone as soon as possible after the first addition of dimethylzinc.

Ethyl 3-hydroxy-3-(2-naphthyl)butanoate (2f)\(^4\)

\[
\text{\begin{align*}
\text{HO} & \quad \text{Me} \\
\text{OEt} & \quad \text{Me}
\end{align*}}
\]

\(2f\) was obtained following the general procedure, after purification by flash chromatography (pentane:Et\(_2\)O 3:1), as a colorless oil (73% yield, 76% ee). Analytical data are in accordance with the lit.\(^4\)

[\([\alpha]_D = -17 \ (c = 1.65, \text{CHCl}_3)\].

Ee determination by chiral HPLC analysis, Chiralpak AD column, Heptane:i-PrOH 99:5, retention times: 8.1 min (major), 9.7 min (minor).

Ethyl 3-(2-furyl)-3-hydroxybutanoate (2g)\(^4\)

\[
\text{HO} \quad \text{Me} \\
\text{OEt} \quad \text{O}
\]

\(2g\) was obtained following the general procedure, after purification by flash chromatography (pentane:Et\(_2\)O 3:1), as a colorless oil (60% yield, 50% ee). Analytical data are in accordance with the lit.\(^4\)

[\([\alpha]_D = -5 \ (c = 1.3, \text{CHCl}_3)\].

Ee determination by chiral HPLC analysis, Chiralpack AD column, Heptane:i-PrOH 99:5, retention times: 8.1 min (major), 9.7 min (minor).

Ethyl 3-hydroxy-3-(2-thienyl)butanoate (2h)\(^5\)

\[
\text{HO} \quad \text{Me} \\
\text{OEt} \quad \text{S}
\]

\(2h\) was obtained following the general procedure, after purification by flash chromatography (pentane:Et\(_2\)O 3:1), as a colorless oil (79% yield, 77% ee).

[\([\alpha]_D = -11.3 \ (c = 2.1, \text{CHCl}_3)\].

\(^{1}H\)-NMR \(\delta\): 1.17 (t, \(J = 7.0\) Hz, 3H), 1.61 (s, 3H), 2.79 (d, \(J = 15.9\) Hz, 1H), 2.96 (d, \(J = 15.9\) Hz, 1H), 4.09 (q, \(J = 7.0\) Hz, 2H), 4.73 (s, 1H), 6.86-6.91 (m, 2H), 7.14-7.16 (m, 1H).

\(^{13}C\)-NMR \(\delta\): 13.9, 31.2, 46.8, 60.7, 71.7, 121.8, 123.8, 126.5, 152.1, 172.2.

MS (Cl) \(m/z\): 214 (M\(^+\)), 199, 151, 127 (100), 111; HRMS calcd for C\(_{10}\)H\(_{14}\)O\(_3\)S (M\(^+\)): 214.0664; found: 214.0675.

Ee determination by chiral HPLC analysis, Chiralcel OD column, Heptane:i-PrOH 98:2, retention times: 8.7 min (minor), 10.6 min (major).

Ethyl 3-hydroxy-3-methyl-5-phenylpent-4-enoate (2i)\(^4\)

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

\(2i\) was obtained following the general procedure, after purification by flash chromatography (pentane:Et\(_2\)O 3:1), as a colorless oil (89% yield, 50% ee). Analytical data are in accordance with the lit.\(^4\)

[\([\alpha]_D = +9.5 \ (c = 2.6, \text{CHCl}_3)\].

Ee determination by chiral HPLC analysis, Chiralcel OD-H column, Heptane:i-PrOH 95:5, flow 0.5 mL/min, retention times: 12.4 min (minor), 13.2 min (major).

(3R) Ethyl 3-hydroxy-3-methylhex-4-enoate (2j)\(^4\)

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

\(2j\) was obtained following the general procedure, after purification by flash chromatography (pentane:Et\(_2\)O 5:2), as a colorless oil (72% yield, 48% ee). Analytical data are in accordance with the lit.\(^4\)

[\([\alpha]_D = -6.1 \ (c = 1.5, \text{CHCl}_3)\]. Lit.\(^4\)\[\([\alpha]_D = -10 \ (c = 1.1, \text{CHCl}_3)\], optical purity 75%.

Ee determination by chiral GC analysis, Chiralsil Dex-CB column, 95 °C isothermic, then 3°C/min, retention times: 19.3 min (R), 20.2 min (S).

Ethyl 3-hydroxy-3,4-dimethylpentanoate (2k)\(^4\)

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

\(2k\) was obtained following the general procedure, after purification by flash chromatography (pentane:Et\(_2\)O 5:2), as a colorless oil (53% yield, 28% ee). Analytical data are in accordance with the lit.\(^4\)

[\([\alpha]_D = +1.5 \ (c = 1.1, \text{CHCl}_3)\].

Ee determination by chiral GC analysis, Chiraldex G-TA column, 93 °C isothermic, retention times: 26.1 min (major), 27.3 min (minor).

Ethyl (1-hydroxy-2,2-dimethylcyclopentyl)acetate (2l)

2l was obtained following the general procedure, after purification by flash chromatography (pentane:EtO 3:1), as a colorless oil (85% yield, 80% ee). Analytical data are in accordance with the lit.\textsuperscript{a} 

\[ \text{[\(\alpha\)]D} = +9.9 \text{ (c = 2.0, CHCl}_3) \].

\( Ee \) determination by chiral GC analysis, Chiralsil Dex-CB column, T = 80 °C for 50 min, then 5 °C/min to 175 °C, retention times: 63.8 min (major), 64.2 min (minor).

Ethyl 3-hydroxy-3-(2-methylphenyl)-3-phenylpropanoate (2m)

2m was obtained following the general procedure, after purification by flash chromatography (pentane:EtO 5:1), as a colorless oil (40% yield, 82% ee).

\[ \text{[\(\alpha\)]D} = +76.6 \text{ (c = 1.2, CHCl}_3) \].

\(^1\text{H-NMR} \delta 1.21 (t, J = 7.3 \text{ Hz}, 3H), 2.12 (s, 3H), 3.02 (d, J = 16.1 \text{ Hz}, 1H), 3.36 (d, J = 16.1 \text{ Hz}, 1H), 4.10-4.23 (m, 2H), 5.25 (s, 1H), 7.11-7.43 (m, 9H). \\
\(^{13}\text{C-NMR} \delta 13.7, 21.2, 46.3, 60.7, 76.3, 124.6, 125.1, 125.3, 126.5, 127.4, 127.6, 132.5, 137.9, 142.2, 145.4, 172.8. \\
\]

\text{MS (Cl)} m/z: 266 (M\textsuperscript{+}-18), 197, 178, 119, 105 (100); HRMS calcd for C\textsubscript{18}H\textsubscript{20}O\textsubscript{3} (M\textsuperscript{+}): 284.1413; found: 284.1433.

\( Ee \) determination by chiral HPLC analysis, Chiralcel OJ-H column, Heptane:i-PrOH 97:3, retention times: 23.3 min (minor), 30.3 min (major).