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Supporting Information

Counterion Enhanced Organocatalysis: A Novel Approach for the Asymmetric Transfer Hydrogenation of Enones

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1. General remarks

All purchased chemicals from commercial suppliers were used without further purification. Dry solvents were pre-distilled and desiccated on aluminium oxide columns (PURESOLV, Innovative Technology).

Column chromatography was performed on standard manual glass columns using Merck (40-60 µm) silica gel with pre-distilled solvents (PE : petrolether, EtOAc : ethyl acetate, Et₂O : diethyl ether). For TLC analysis, precoated aluminium-backed plates were purchased from Merck (silica gel 60 F₂₅₄). UV active compounds were detected at 254 nm. Non-UV active compounds have been detected using vanillin staining solution (5% vanillin in EtOH + H₂SO₄).

¹H, ¹³C, and ³¹P NMR spectra were recorded on a Bruker Advance UltraShield 200 MHz or 400 MHz spectrometer and chemical shifts are reported in ppm using TMS (tetramethylsilane) as internal standard. Coupling constants (J) are given in Hz. For NMR purpose, the following abbreviations are used: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), brs (broad singlet), dd (doublet of doublets), ddd (doublets of doublet of doublets), td (triplet of doublets), dt (doublet of triplets).

GC analysis have been performed on a Thermo Scientific Focus on BGB5 column by using FID detector. Chiral GC measurements were performed on chiral BGB columns (BGB173 or BGB175) by using FID detector.

Chiral HPLC measurements were carried out on a DIONEX UPLC equipped with a photodiode array (PDA) plus detector (190–360 nm), using a Diacel Chiralcel AS-H column (250×4.60 mm, 5 µm).

Optical rotation was measured on an Anton Paar MCP500 polarimeter at the specific conditions and the results have been compared to literature values. Concentrations are given in g / 100 ml.

HR-MS analysis was performed using HTC PAL system auto sampler, an Agilent 1100/1200 HPLC and Agilent 6230 AJS ESI-TOF mass spectrometer.

Microwave reactions were performed on a Biotage Initiator Classic in 20 ml pressure tight glass vials.

Melting points above room temperature were measured on an automated melting point system OPTI MELT of Stanford Research Systems and are uncorrected.

Infrared spectra were recorded on a Perkin-Elmer Spectrum 65 FT IR spectrometer equipped with a specac MK II Golden Gate Single Reflection ATR unit.
2. Synthesis of L-amino acid derivatives

2.1 General procedure for the synthesis of L-amino acid tert-butyl esters

Compound have been prepared by the following literature procedure:

To a solution of the corresponding L-amino acid (1.0 equiv.) in tert-butyl acetate (18.0 equiv.), HClO\textsubscript{4} (60 % aqueous solution, 1.5 equiv.) was added dropwise at 0°C. The reaction mixture was stirred 18 h at room temperature. Distilled H\textsubscript{2}O was added, and the reaction mixture was extracted with distilled H\textsubscript{2}O (2 \times) and 1 N HCl (3 \times). The combined aqueous phases were then adjusted to pH 10 with a saturated Na\textsubscript{2}CO\textsubscript{3} solution. The resulting solution was then extracted with CH\textsubscript{2}Cl\textsubscript{2}. The combined organic phases were dried over anhydrous Na\textsubscript{2}SO\textsubscript{4} and concentrated under reduced pressure to give the L-amino acid tert-butyl esters, which were find to be pure without further purifications.

**tert-Butyl L-valinate**

Light yellow oil (67% yield). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 3.17 (d, \(J = 4.8\) Hz, 1H, CH-NH\textsubscript{2}), 2.03 – 1.97 (m, 1H, CH-(CH\textsubscript{3})\textsubscript{3}), 1.57 (s, 2H, NH\textsubscript{2}), 1.46 (s, 9H, 3 \times CH\textsubscript{3}-C), 0.97 (d, \(J = 6.9\) Hz, 3H, CH\textsubscript{3}-CH), 0.89 (d, \(J = 6.9\) Hz, 3H, CH\textsubscript{3}-CH).

**tert-Butyl L-leucinate**

Light yellow oil (69% yield). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 3.26 (t, \(J = 8.0\) Hz, 1H, CH-NH\textsubscript{2}), 1.74 – 1.67 (m, 1H, CH-(CH\textsubscript{3})\textsubscript{3}), 1.48 – 1.37 (m, 12H, CH\textsubscript{2a}-CH-NH\textsubscript{2}, NH\textsubscript{2}, 3 \times CH\textsubscript{3}-C), 1.33 – 1.27 (m, 1H, CH\textsubscript{2b}-CH-NH\textsubscript{2}), 0.86 (t, \(J = 9.0\) Hz, 6H, 2 \times CH\textsubscript{2}-CH).

**tert-Butyl L-isoleucinate**

Light yellow oil (36% yield). \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 3.22 (d, \(J = 4.8\) Hz, 1H, CH-NH\textsubscript{2}), 1.73 – 1.67 (m, 1H, CH-CH\textsubscript{3}), 1.48 (s, 2H, NH\textsubscript{2}), 1.46 (s, 9H, 3 \times CH\textsubscript{3}-C), 1.12 – 1.23 (m, 2H, CH\textsubscript{2}-CH\textsubscript{3}), 1.12 – 0.70 (m, 6H, 2 \times CH\textsubscript{3}).
**tert-Butyl-(S)-2-amino-2-phenylacetate**

Light yellow solid (61% yield). \( ^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.30 – 7.16 (m, 5H, H-arom), 4.39 (s, 1H, CH-NH\(_2\)), 1.99 (s, 2H, NH\(_2\)), 1.30 (s, 9H, 3 × CH\(_3\)-C).

**tert-Butyl L-phenylalaninate**

Light yellow oil (65% yield). \( ^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.23 – 7.14 (m, 5H, H-arom), 3.54 (t, J = 7.8 Hz, 1H, CH-NH\(_2\)), 2.97 (dd, J = 16.0 Hz, 8.0 Hz, 1H, CH\(_{2a}\)-CH-NH\(_2\)), 2.77 (dd, J = 16.0 Hz, 8.0 Hz, 1H, CH\(_{2b}\)-CH-NH\(_2\)), 1.40 (s, 2H, NH\(_2\)), 1.35 (s, 9H, 3 × CH\(_3\)-C).

**tert-Butyl (S)-2-amino-3,3-dimethylbutanoate**

Light yellow oil (72% yield). \( ^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 2.95 (s, 1H, CH-NH\(_2\)), 1.41 (s, 11H, NH\(_2\), 3 × CH\(_3\)-C), 0.90 (s, 9H, 3 × CH\(_3\)-C).
2.2 General procedure for the synthesis of L-amino acid esters via DCC/DMAP coupling

L-Valine mentyl esters (all three diastereomers), L-valine cyclohexyl ester and L-valine 4-( tert-butyl)cyclohexyl ester have been prepared by the following two step general procedure:  

\[
\begin{align*}
\text{NH}_2 \quad \text{OH} & \quad \xrightarrow{(\text{Boc})_2\text{O} \\
2\text{M NaOH}, \text{RT}, 18\text{h}} \quad \text{HN}^\text{Boc} \quad \text{OH} & \quad \xrightarrow{1) \text{R}_2\text{OH} \quad \text{DCC, DMAP} \\
\text{CH}_2\text{Cl}_2, \text{RT}, 18\text{h}} \quad \text{HN} \quad \text{O} \quad \text{R}_2 & \quad \xrightarrow{2) 4\text{M HCl/Dioxane} \\
3) 10\% \text{NaHCO}_3 & \quad \text{NH}_2 \quad \text{OH}
\end{align*}
\]

A solution of L-valine (5.0 g, 43 mmol, 1.0 equiv.) in 2 N NaOH (43 mL) was cooled to 0°C and Boc\(_2\)O (11.3 g, 51.6 mmol, 1.2 equiv.) was added slowly via syringe. The ice bath was removed and the reaction mixture stirred for 18 h at room temperature. The mixture was acidified (pH = 2) by using a 4 N HCl and extracted with EtOAc (3 × 50 mL). The combined organic phases were dried over anhydrous Na\(_2\)SO\(_4\) and concentrated to give (tert-butoxycarbonyl)-L-valine as a colorless oil (8.3 g, 90%).

To a solution of (tert-butoxycarbonyl)-L-valine (1.0 equiv.) in dry CH\(_2\)Cl\(_2\), DCC (1.1 equiv.) was added at room temperature. The suspension was cooled to 0°C followed by the addition of the corresponding alcohol (1.0 equiv.) and DMAP (0.1 equiv.). The reaction mixture was stirred for 18 h at room temperature followed by the addition of EtOAc. After 10 min of stirring, the dicyclohexyl urea was filtered off, rinsed with EtOAc and the filtrate was successively washed with 1 N HCl solution, saturated NaHCO\(_3\) solution, dried over anhydrous Na\(_2\)SO\(_4\) and concentrated under reduced pressure. 4 N HCl in dioxane was added and the resulting mixture was stirred for 3 h at room temperature. The solvent was removed, Et\(_2\)O was added and stirred for 10 min. The amino acid HCl salt was filtered off, washed with Et\(_2\)O (3×) and dried in vacuo. The salt was suspended in CH\(_2\)Cl\(_2\), saturated NaHCO\(_3\) was added and stirred for 2 h at room temperature. The organic phase was separated, washed with saturated NaHCO\(_3\) (3×) and concentrated under reduced pressure to yield the corresponding esters.

*Menthy valinates (all diastereomers)*

Colorless oil (DL: 58% yield, D: 55% yield, L: 58% yield). \(^1\text{H NMR (400 MHz, CDCl\(_3\)) δ}\)

4.73 (td, \(J = 10.9, 4.4\) Hz, 1H, CH-\(\text{O}\)), 3.29 (d, \(J = 4.8\) Hz, 1H, CH-NH\(_2\)), 2.15 – 2.01 (m, 1H, CH-(CH\(_3\))\(_2\)), 2.00 – 1.01 (m, 10H, NH\(_2\), H-menthol), 0.99 (d, \(J = 6.9\) Hz, 3H, CH\(_3\)-CH), 0.90 (m, 9H, 2 × CH\(_3\)-CH, CH\(_3\)-CH-menthol), 0.76 (d, \(J = 7.0\) Hz, 3H, CH\(_3\)-menthol); \(^{13}\text{C NMR (100 MHz, CDCl\(_3\)) δ}\)

175.30, 74.88, 60.40, 47.08, 41.01, 34.37, 31.90, 31.53, 26.11, 23.09, 22.15, 21.01, 19.79, 16.65, 15.89.
4-(tert-Butyl)cyclohexyl-L-valinate

Colorless oil (18% yield). \(^1\text{H NMR (400 MHz, CDCl}_3\) δ 4.73 – 4.66 (m, 1H, CH-O), 3.30 (d, \(J = 4.8\) Hz, 1H, CH-NH\(_2\)), 2.25 (s, 2H, NH\(_2\)), 2.12 – 1.94 (m, 3H, CH-(CH\(_3\))\(_2\), CH\(_2\)-CH-O), 1.85 – 1.75 (m, 2H, CH\(_2\)-CH-O), 1.41 – 1.22 (m, 2H, CH\(_2\)-CH-C-tbu), 1.18 – 1.00 (m, 2H, CH\(_2\)-CH-C-tbu), 0.99 (d, \(J = 6.9\) Hz, 3H, CH\(_3\)-CH), 0.92 (d, \(J = 6.9\) Hz, 3H, CH\(_3\)-CH), 0.85 (s, 9H, 3 \(\times\) CH\(_3\)-C).

Cyclohexyl-L-valinate

Colorless oil (49% yield). \(^1\text{H NMR (400 MHz, CDCl}_3\) δ 4.93 – 4.64 (m, 1H, CH-O), 3.24 (d, \(J = 4.9\) Hz, 1H, CH-NH\(_2\)), 2.05 – 1.97 (m, 1H, CH-(CH\(_3\))\(_2\)), 1.81 (bs, 2H, NH\(_2\)), 1.74 – 1.00 (m, 10H, CH-cyclohexyl), 0.96 (d, \(J = 6.9\) Hz, 3H, CH\(_3\)-CH), 0.88 (d, \(J = 6.9\) Hz, 3H, CH\(_3\)-CH).
2.3 Synthesis of other L-amino acid esters

**Methyl L-valinate**

![Methyl L-valinate reaction scheme]

To a slurry of L-valine methyl-ester hydrochloride (1.27 g, 7.6 mmol, 1.0 equiv.) in dry MeOH (1 mL), Et₃N (1.6 mL, 12 mmol, 1.6 equiv.) was added. After 10 min of stirring, dry Et₂O (30 mL) was added, the solution was cooled to 0°C and it was stirred for another 30 min. The triethylamine hydrochloride salt was filtered off and the filtrate was concentrated to yield the product as a colorless oil (800 mg, 81%).

**¹H NMR (400 MHz, CDCl₃)** δ 3.70 (s, 3H, CH₃-O), 3.28 (d, J = 5.1 Hz, 1H, CH-NH₂), 2.11 – 1.93 (m, 1H, CH-(CH₃)₂), 1.45 (s, 2H, NH₂), 0.95 (d, J = 6.9 Hz, 3H, CH₃-CH), 0.88 (d, J = 6.9 Hz, 3H, CH₃-CH).

**Isopropyl L-valinate**

![Isopropyl L-valinate reaction scheme]

To a solution of L-valine (1.0 g, 8.5 mmol, 1.0 equiv.) in isopropanol (26 mL, 341 mmol, 40 equiv.) was added thionyl chloride (3.1 mL, 43 mmol, 5.0 equiv.) at 0°C. The reaction mixture was then refluxed for 18 h. After cooling to room temperature, the solvent was evaporated, Et₂O (50 mL) was added and the amino acid hydrochloride salt was filtered off. CH₂Cl₂ (50 mL) was added, followed by the addition of sat. NaHCO₃ (50 mL) and the two phases were stirred for 30 min. The organic phase was washed several times with sat. NaHCO₃ (3 × 25 mL), dried over anhydrous Na₂SO₄ and concentrated to give the product as a colorless liquid (380 mg, 23%).

**¹H NMR (400 MHz, CDCl₃)** δ 5.09 – 5.02 (m, 1H, CH-O), 3.26 (d, J = 4.9 Hz, 1H, CH-NH₂), 2.07 – 1.99 (m, 1H, CH-(CH₃)₂), 1.82 (s, 2H, NH₂), 1.42 – 1.16 (m, 6H, 2 x CH₃-CH-O), 0.98 (d, J = 6.9 Hz, 3H, CH₃-CH), 0.91 (d, J = 6.9 Hz, 3H, CH₃-CH).

**Benzyl L-valinate**

![Benzyl L-valinate reaction scheme]

To a solution of L-valine (1.0 g, 8.5 mmol, 1.0 equiv.) in benzyl alcohol (26 mL, 341 mmol, 40 equiv.) was added thionyl chloride (3.1 mL, 43 mmol, 5.0 equiv.) at 0°C. The reaction mixture was then stirred for 18 hours at room temperature. Et₂O (50 mL) was added and the amino acid hydrochloride salt was
filtered off. CH₂Cl₂ (50 mL) was added, followed by the addition of sat. NaHCO₃ (50 mL) and the two phases were stirred for 30 min. The organic phase was washed several times with sat. NaHCO₃ (3 × 25 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure to give the product as a colorless liquid (1.12 g, 62%). 

**¹H NMR (400 MHz, CDCl₃)** δ 7.37 – 7.32 (m, 5H, H-arom), 5.15 (dd, J = 12.0 Hz, 16.0 Hz, 1H, CH₂-arom), 3.34 (d, J = 4.0 Hz, 1H, CH-NH₂), 2.08 – 2.01 (m, 1H, CH-(CH₃)₂), 1.68 (s, 2H, NH₂), 0.96 (d, J = 6.9 Hz, 3H, CH₃-CH), 0.88 (d, J = 6.9 Hz, 3H, CH₃-CH).
3. General synthesis of the phosphoric acids

The phosphoric acids have been prepared following either a one or a two-step reaction pathway:

1.) One step procedure: 

To a solution of the corresponding diol (1.0 equiv.) in dry Et₂O or THF, pyridine (2.0 equiv.) was added. The reaction mixture was cooled to 0°C and POCl₃ (1.4 equiv.) was added slowly via syringe. The resulting reaction mixture was stirred for 18 h at room temperature. The pyridinium hydrochloride was filtered off and it was rinsed several times with Et₂O. The filtrate was concentrated and recrystallized from n-heptane. The white solid was filtered off, washed with n-heptane (3×) and hydrolyzed with 6 N HCl for 3 h at reflux temperature. Filtration gave the products as a white solid.

6-Hydroxydibenzo[d,f][1,3,2]dioxaphosphepine 6-oxide

White solid (81% yield). H NMR (400 MHz, DMSO-d₆) δ 7.63 (dd, J = 7.6, 1.7 Hz, 2H, H-arom), 7.50 (td, J = 7.8, 1.7 Hz, 2H, H-arom), 7.39 (tt, J = 7.5, 1.3 Hz, 2H, H-arom), 7.32 – 7.21 (m, 2H, H-arom); P NMR (162 MHz, DMSO-d₆) 1.72. Analytical data were in accordance with the literature.

4-Hydroxydinaphtho[2,1-d:1',2'-f][1,3,2]dioxaphosphepine 4-oxide

White solid ((S,R): 89% yield, (R): 93% yield, (S): 94% yield). H NMR (400 MHz, DMSO-d₆) δ 8.18 (d, J = 8.9 Hz, 2H, H-arom), 8.08 (d, J = 1.3 Hz, 2H, H-arom), 7.52 (ddd, J = 8.1, 6.7, 1.2 Hz, 2H, H-arom); 31P NMR (162 MHz, DMSO-d₆) 2.66. Analytical data were in accordance with the literature.
2.) Two step procedure:  

In a 20 mL microwave vial equipped with a stir bar, the corresponding phenol (1.0 equiv.) was dissolved in chlorobenzene (1.66 M). Di-tert-butyl peroxide (1.05 equiv.) was then added via syringe. The vial was capped and the reaction mixture was stirred for 15 min at room temperature. The vial was then placed in the microwave reactor and heated to 160°C (high absorption setting) and stirred for 15 min. The reaction mixture was allowed to cool down and volatiles have been removed under reduced pressure. The resulting crude mixture was purified by column chromatography (EtOAc: PE, UV visualization) to afford the desired 2,2'-diols (Step A).

To a solution of the corresponding 2,2'-diol (1.0 equiv.) in pyridine, POCl₃ (2.0 equiv.) was added slowly via syringe at 0°C. After stirring the reaction mixture for 24 h at 95°C, it was cooled to room temperature and distilled H₂O was added slowly. The resulting clear solution was stirred for another 18 h at 95 °C. After cooling down to room temperature, 4 N HCl was added slowly. The precipitate of the product was filtered off and washed with 4 N HCl. The solid product was further hydrolyzed by redissolving it in CH₂Cl₂ and washing several times with 4 N HCl (3-4×) After being dried over anhydrous Na₂SO₄, removal of the solvent gave the phosphoric acids (Step B).

3,3’-Di-tert-butyl-5,5’-dimethyl-[1,1’-biphenyl]-2,2’-diol (Step A) ¹¹

Column chromatography (1.5% EtOAc in light petrol) afforded the product as pale yellow solid (53% yield). ¹H NMR (400 MHz, CDCl₃) δ 7.20 (d, J = 2.1 Hz, 2H, H-arom), 6.94 (d, J = 2.1 Hz, 2H, H-arom), 5.24 (s, 2H, 2 × OH), 2.36 (s, 6H, 2 × CH₃), 1.48 (s, 18H, 6 × CH₃-C).
3,3'-Diisopropyl-6,6'-dimethyl-[1,1'-biphenyl]-2,2'-diol (STEP A) 12

Column chromatography (2% EtOAc in light petrol) afforded the product as light yellow oil (58% yield). 1H NMR (400 MHz, CDCl3) δ 7.19 (d, J = 7.7 Hz, 2H, H-arom), 6.89 (d, J = 7.8 Hz, 2H, H-arom), 4.76 (s, 2H, 2 × OH), 3.32 – 3.25 (m, 2 × CH(CH3)2), 1.96 (s, 6H, 2 × CH3), 1.26 (dd, J = 6.9, 2.7 Hz, 12H, 4 × CH(CH3)-CH); 13C NMR (100 MHz, CDCl3) δ 150.99, 135.67, 132.57, 126.75, 122.22, 119.38, 27.17, 22.64, 22.50, 19.26.

3,3'-Di-tert-butyl-6,6'-dimethyl-[1,1'-biphenyl]-2,2'-diol (STEP A) 13

Column chromatography (1.5% EtOAc in light petrol) afforded the product as white solid (45% yield). 1H NMR (400 MHz, CDCl3) δ 7.27 (d, J = 8.0 Hz, 2H, H-arom), 6.87 (d, J = 8.0 Hz, 2H, H-arom), 5.01 (s, 2H, 2 × OH), 1.94 (s, 6H, 2 × CH3), 1.42 (s, 18H, 6 × CH3-C); 13C NMR (100 MHz, CDCl3) δ 152.35, 134.08, 127.50, 121.97, 120.26, 34.79, 29.64, 19.28.

4,8-Di-tert-butyl-6-hydroxy-2,10-dimethyldibenzo[d,f][1,3,2]dioxaphosphepine 6-oxide (STEP B) 14

Grey solid (63% yield). 1H NMR (400 MHz, CDCl3) δ 7.26 (s, 2H, H-arom), 7.02 (s, 2H, H-arom), 2.36 (s, 6H, 2 × CH3), 1.50 (s, 18H, 6 × CH3-C); 31P NMR (162 MHz, CDCl3) δ 0.48. Analytical data were in accordance with the literature.15

6-Hydroxy-4,8-diisopropyl-1,11-dimethyldibenzo[d,f][1,3,2]dioxaphosphepine-6-oxide (STEP B)

Brown solid (85% yield). 1H NMR (400 MHz, CDCl3) δ 7.27 (d, J = 8.0 Hz, 2H, H-arom), 7.15 (d, J = 8.0 Hz, 2H, H-arom), 3.49 – 3.45 (m, 2H, 2 × CH(CH3)2), 2.14 (s, 6H, 2 × CH3), 1.27 (dd, J = 25.5, 6.9 Hz, 12H, 4 × CH3-CH); 31P NMR (162 MHz, CDCl3) δ 2.40; 13C NMR (100 MHz, CDCl3) δ 145.40, 137.74, 136.08, 128.02, 127.11, 126.31, 26.60, 24.10, 22.75, 19.67; IR ATR (vmax/cm⁻1) 2963 (O-H), 2872 (C-H), 1610 (C=O), 967 (C-H), 818 (C-H arom); HRMS (ESI-TOF) [M + Na]+ calc. 383.1388, found 383.1389.
4,8-Di-tert-butyl-6-hydroxy-1,11-dimethyl dibenzo[d,f][1,3,2]dioxaphosphepine 6-oxide (STEP B)

White solid (66% yield). $^1$H NMR (400 MHz, CDCl$_3$) δ 7.38 (dd, $J = 8.0$, 1.5 Hz, 2H, H-arom), 7.11 (dd, $J = 11.8$, 8.2 Hz, 2H, H-arom), 2.01 (d, $J = 27.3$ Hz, 6H, 2 $\times$ CH$_3$), 1.48 (d, $J = 12.4$ Hz, 18H, 6 $\times$ CH$_3$-C); $^{31}$P NMR (162 MHz, CDCl$_3$) δ 3.99; $^{13}$C NMR (100 MHz, CDCl$_3$) δ 144.48, 144.31, 140.81, 140.72, 134.81, 130.10, 129.91, 128.89, 35.18, 31.26, 21.10; IR ATR ($\nu_{\text{max}}$/cm$^{-1}$) 2961 (O-H), 2872 (C-H), 1610 (C=C), 1308 (C-O), 1023 (C-H), 901 (C-H arom); HRMS (ESI-TOF) [M + Na]$^+$ calc. 411.1701, found 411.1732.
4. **Synthesis of the Hantzsch ester**

*Diethyl 2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylate*\(^{16}\)

\[
\begin{align*}
&\text{O} &\text{O} &\text{Et} &\xrightarrow{\text{NH}_2\text{OAc}} &\text{Et} &\text{O} &\text{N}
\end{align*}
\]

Compound was prepared by the following modified literature procedure.

A mixture of formaldehyde (37% aqueous solution, 4.0 g, 49 mmol, 1.0 equiv.), NH\(_4\)OAc (7.6 g, 99 mmol, 2.0 equiv.), ethyl acetoacetate (26 g, 0.2 mol, 4.0 equiv.) and distilled H\(_2\)O (100 mL) was refluxed at 90°C for 18 h. After cooling the reaction mixture to room temperature, cold distilled H\(_2\)O (100 mL) was added, the crude product was filtered off, washed with cold distilled H\(_2\)O (100 mL) and dried in vacuo. Recrystallization from MeOH gave the product as a yellow solid (7.5 g, 60%). \(^1\)H NMR \((400\) MHz, CDCl\(_3\)) \(\delta\) 5.19 (s, 1H, NH), 4.16 (q, \(J = 7.1\) Hz, 4H, \(2 \times CH_2\)-O), 3.26 (s, 2H, CH\(_2\)), 2.19 (s, 6H, \(2 \times CH_3\)), 1.28 (t, \(J = 7.1\) Hz, 6H, \(2 \times CH_3-CH_2\)-O).
5. Synthesis of ATH substrates

3-Methyl-2-cyclohexenone, 3-methyl-cyclopentenone and isophorone have been purchased from commercial supplier (Sigma Aldrich).

The remaining 3-alkylcyclohexenones and 3-arylcyclohexanones have been prepared by the following procedure, starting from 3-ethoxycyclohexenone (Acros Organics): 17

A 3 M solution of the Grignard reagent was prepared freshly from freshly ground Mg (1.0 equiv.), alkyl/aryl bromide (1.0 equiv.) in dry THF, and it was refluxed for 1 h. After being cooled to 0°C, 3-ethoxycyclohexenone (1.0 equiv.) was added slowly and the reaction mixture was stirred for 18 h at room temperature. The reaction was quenched with 1 N HCl solution (50 mL) at 0°C. Et₂O was added and the organic phase was washed with 1 N HCl solution (3 × 25 mL), sat. NaHCO₃ (3 × 25 mL), dried over anhydrous Na₂SO₄ and concentrated under reduced pressure. The crude products were purified by column chromatography (Et₂O: PE, UV TLC visualization) to provide the pure products.

3-Ethyl-2-cyclohexenone 18

Column chromatography (25% Et₂O in PE) afforded the product as a yellow oil (67% yield). 1H NMR (400 MHz, CDCl₃) δ 5.87 (s, 1H, CH), 2.45 – 2.11 (m, 6H, CH₂-CO, CH₂-CH₂-CO, CH₂-C-ethyl), 2.07 – 1.81 (m, 2H, CH₃-CH₂), 1.09 (t, J = 7.4 Hz, 3H, CH₃).

3-Propyl-2-cyclohexenone 19

Column chromatography (25% Et₂O in PE) afforded the product as a yellow oil (60% yield). 1H NMR (400 MHz, CDCl₃) δ 5.87 (s, 1H, CH), 2.53 – 2.07 (m, 6H, CH₂-CO, CH₂-CH₂-CO, CH₂-C-propyl), 2.07 – 1.73 (m, 2H, CH₃-CH₂-CH₃), 1.68 – 1.36 (m, 2H, CH₂-CH₃), 0.93 (t, J = 7.4 Hz, 3H, CH₃).
3-Butyl-2-cyclohexenone \(^{20}\)

Column chromatography (30% Et\(_2\)O in PE) afforded the product as a yellow oil (74% yield). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 5.86 (s, 1H, CH), 2.48 – 2.09 (m, 6H, CH\(_2\)-CH\(_2\)-CO, CH\(_2\)-CH\(_2\)-C-butyl), 2.06 – 1.79 (m, 2H, CH\(_2\)-CH\(_2\)-CH\(_3\)-CH\(_3\)), 1.61 – 1.15 (m, 4H, CH\(_2\)-CH\(_2\)-CH\(_3\)-CH\(_3\)), 0.91 (t, \(J = 7.0\) Hz, 3H, CH\(_3\)).

3-Isobutyl-2-cyclohexenone \(^{21}\)

Column chromatography (25% Et\(_2\)O in PE) afforded the product as a yellow oil (69% yield). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 5.84 (s, 1H, CH), 2.54 – 2.17 (m, 4H, CH\(_2\)-CO, CH\(_2\)-CH\(_2\)-CO), 2.18 – 1.56 (m, 5H, CH\(_2\)-CH\(_3\)-isobutyl, CH\(_2\)-CH(CH\(_3\))\(_2\), CH\(_2\)-CH(CH\(_3\))\(_2\)), 0.90 (d, \(J = 6.5\) Hz, 6H, 2 \times CH\(_3\)-CH).

3-Isopropyl-2-cyclohexenone \(^{22}\)

Column chromatography (25% Et\(_2\)O in PE) afforded the product as a yellow oil (10% yield). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 5.88 (s, 1H, CH), 2.61 – 2.17 (m, 5H, CH\(_2\)-CO, CH\(_2\)-CH\(_2\)-CO, CH\(_2\)-CH\(_3\)-CH\(_3\)), 2.13 – 1.81 (m, 2H, CH\(_2\)-C-isopropyl), 1.10 (d, \(J = 6.9\) Hz, 6H, 2 \times CH\(_3\)-CH).

3-Phenyl-2-cyclohexenone \(^{23}\)

Column chromatography (30% Et\(_2\)O in PE) afforded the product as a white solid (88% yield). \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.53 – 7.41 (m, 5H, H-arom), 6.42 (s, 1H, CH), 2.85 – 2.78 (m, 2H, CH\(_2\)-CO), 2.62 – 2.49 (m, 2H, CH\(_2\)-CH\(_2\)-CO), 2.18 – 2.14 (m, 2H, CH\(_2\)-C-phenyl).

3-Phenethyl-2-cyclohexenone \(^{24}\)

The formation of the grignard-reagent and the reaction have been carried out at 40°C. Column chromatography (30% Et\(_2\)O in PE) afforded the product as a light yellow oil (91% yield). \(^1\)H NMR (200 MHz, CDCl\(_3\)) \(\delta\) 7.34 – 7.15 (m, 5H, H-arom), 5.90 (s, 1H, CH), 2.89 – 2.76 (m, 2H, CH\(_2\)-CO), 2.58 – 2.47 (m, 2H, CH\(_2\)-CH\(_2\)-CO), 2.40 – 2.26 (m, 4H, phenyl-CH\(_2\)-CH\(_3\)) 2.05 – 1.92 (m, 2H, CH\(_2\)-C-phenyl).

S16
3-(Naphtalen-1-yl)-2-cyclohexenone ²⁵

Column chromatography (30% - 50% Et₂O in PE) afforded the product as a yellow oil (94% yield). \(^1\)H NMR (200 MHz, CDCl₃) \(\delta\) 7.92 – 7.82 (m, 3H, H-arom), 7.54 – 7.45 (m, 3H, H-arom), 7.35 – 7.28 (m, 1H, H-arom), 6.21 (s, 1H, CH), 2.82 – 2.74 (m, 2H, CH₂-CO), 2.64 – 2.56 (m, 2H, CH₂-CH₂-CO), 2.33 – 2.19 (m, 2H, CH₂-C-arom).

3-Piperonyl-2-cyclohexenone ²⁶

Column chromatography (30% Et₂O in PE) afforded the product as a yellow foam (90% yield). \(^1\)H NMR (200 MHz, CDCl₃) \(\delta\) 7.06 (ddd, \(J = 8.0\) Hz, 4.0 Hz, 2.0 Hz, 2H, H-arom), 6.83 (d, \(J = 8.0\) Hz, 1H, H-arom), 6.33 (s, 1H, CH), 6.01 (s, 2H, OCH₂), 2.76 – 2.67 (t, \(J = 6.0\) Hz, 2H, CH₂-CO), 2.50 – 2.41 (t, \(J = 6.0\) Hz, 2H, CH₂-CH₂-CO), 2.19 – 2.06 (m, 2H, CH₂-C-arom).
6. General procedure and optimization of the ATH reactions

6.1 General procedures

General procedure for parameter optimization

An 8 mL screw cap vial equipped with a magnetic stir bar was charged with 3-methylcyclohexenone (0.18 mmol, 1.0 equiv.) in the appropriate solvent (0.55 mL, 0.33 M), followed by the addition of the catalyst (0.009 – 0.036 mmol, 5 mol% – 20 mol%) and the appropriate Hantzsch ester (0.22 mmol, 1.2 equiv.). The reaction mixture was stirred at the given temperature for 48 h. The conversion and yield have been determined by GC measurement by using n-dodecane as internal standard, while chiral GC have been used to determine the enantiomeric excess.

General procedure for scope and limitations

A 20 mL microwave vial equipped with a magnetic stir bar was charged with ketone (1.8 mmol, 1.0 equiv.) in MTBE (5.5 mL, 0.33 M), followed by the addition of the catalyst (55.4 mg, 0.09 mmol, 5 mol%) and Hantzsch ester (552 mg, 2.2 mmol, 1.2 equiv.). The reaction mixture was stirred at 50°C for 48 h. After cooling to room temperature, Et₂O (5 mL) and 4 M HCl (10 mL) was added and the mixture was stirred until the phases were transparent (30 min). The phases were separated and the organic phase
was washed with 4 M HCl (3 × 20 mL). The organic phase was dried over Na₂SO₄ and concentrated under reduced pressure. Purification by column chromatography (Et₂O: PE, vanillin staining agent or UV visualization) gave the 3-substituted cyclohexanones.

6.2 Analytical data of ATH products

(S)-3-Methylcyclohexanone

Column chromatography (25% Et₂O in PE) afforded the product as a colorless oil.

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\]

GC yield: 98%, isolated yield: 72% due to high volatility, 95% ee. \([\alpha]^{20}_D: -11.1 (c = 1.0, \text{CHCl}_3)\); \(^1\text{H NMR (400 MHz, CDCl}_3\) \(\delta 2.41 – 2.21 (m, 3H), 2.09 – 1.82 (m, 4H), 1.76 – 1.57 (m, 1H), 1.42 – 1.24 (m, 1H), 1.02 (d, \(J = 6.4 \text{ Hz, 3H)\. Determination of the enantiomeric excess BGB175 column (85°C isotherm 20 min, 30°C/min to 220°C):} t_R (S) = 9.0 \text{ min, } t_R (R) = 9.6 \text{ min.}

(S)-3-Ethylcyclohexanone

Column chromatography (25% Et₂O in light petrol) afforded the product as a colorless oil. GC yield: 85%, isolated yield: 76% due to high volatility, 92% ee. \([\alpha]^{20}_D: -15.6 (c = 1.0, \text{CHCl}_3)\); \(^1\text{H NMR (400 MHz, CDCl}_3\) \(\delta 2.45 – 2.23 (m, 3H), 2.09 – 1.87 (m, 3H), 1.76 – 1.63 (m, 2H), 1.41 – 1.28 (m, 3H), 0.91 (t, \(J = 7.5 \text{ Hz, 3H)\. Determination of the enantiomeric excess BGB173 column (52°C isotherm 110 min, 30°C/min to 220°C):} t_R (R) = 51.0 \text{ min, } t_R (S) = 54.9 \text{ min.}

(S)-3-Propylcyclohexanone

Column chromatography (25% Et₂O in PE) afforded the product as a colorless oil.

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\]

GC yield: 70%, isolated yield: 55% due to high volatility, 91% ee. \([\alpha]^{20}_D: -14.7 (c = 1.0, \text{CHCl}_3)\); \(^1\text{H NMR (400 MHz, CDCl}_3\) \(\delta 2.42 – 2.22 (m, 3H), 2.06 – 1.86 (m, 3H), 1.80 – 1.74 (m, 1H), 1.67 – 1.59 (m, 1H), 1.35 – 1.26 (m, 5H), 0.92 – 0.86 (m, 3H)\. Determination of the enantiomeric excess BGB175 column (70°C isotherm 60 min, 1°C/min to 150 °C, 5 min at 150°C, 30°C /min to 220°C):} t_R (S) = 50.6 \text{ min, } t_R (R) = 53.1 \text{ min.
(S)-3-Butylcyclohexanone

Column chromatography (25% Et₂O in PE) afforded the product as a colorless oil.

GC yield: 91%, isolated yield: 87%, 93% ee. [α]D⁰²₀: −15.0 (c = 1.0, CHCl₃);

1H NMR (400 MHz, CDCl₃) δ 2.44 – 1.56 (m, 7H), 1.40 – 1.09 (m, 7H), 0.91 – 0.82 (m, 4H).

Determination of the enantiomeric excess BGB175 column (70 °C isotherm 60 min, 1°C/min to 150°C, 5 min at 150°C, 30 °C /min to 220°C): tR (S) = 76.9 min, tR (R) = 78.1 min.

(S)-3-Isobutylcyclohexanone

Column chromatography (25% Et₂O in PE) afforded the product as a colorless oil.

GC yield: 85%, isolated yield: 60% due to high volatility, 86% ee. [α]D⁰²₀: −11.3 (c = 1.0, CHCl₃);

1H NMR (400 MHz, CDCl₃) δ 2.42 – 2.21 (m, 2H), 2.03 – 1.61 (m, 4H),
1.66 – 1.41 (m, 2H), 1.33 – 1.10 (m, 3H), 0.89 – 0.84 (m, 6H). Determination of the enantiomeric excess BGB175 column (70 °C isotherm 5 min, 0.5 °C/min to 110°C, 5 min at 110°C, 30°C /min to 220°C): tR (R) = 39.2 min, tR (S) = 40.7 min.

(S)-3-Isopropylcyclohexanone

Column chromatography (25% Et₂O in PE) afforded the product as a colorless oil.

GC yield: 75%, isolated yield: 68% due to high volatility, 88% ee. [α]D⁰²₀: −12.4 (c = 1.0, CHCl₃);

1H NMR (400 MHz, CDCl₃) δ 2.44 – 1.23 (m, 10H), 0.92 (d, J = 6.0 Hz, 3H), 0.90 (d, J = 6.0 Hz, 3H). Determination of the enantiomeric excess BGB175 column (85°C isotherm 20 min, 30°C/min to 220°C): tR (R) = 20.75 min, tR (S) = 20.96 min.

(S)-3,5,5-Trimethylcyclohexanone

Column chromatography (25% Et₂O in PE) afforded the product as a colorless oil.

GC yield: 66%, isolated yield: 60% due to high volatility, 92% ee. [α]D⁰²₀: −11.9 (c = 1.0, CHCl₃);

1H NMR (400 MHz, CDCl₃) δ 2.33 – 2.14 (m, 2H), 1.92 – 1.83 (m, 3H),
1.60 – 1.56 (m, 1H), 1.38 – 1.25 (m, 2H), 1.05 – 1.01 (m, 5H), 0.88 (s, 3H). Determination of the enantiomeric excess BGB175 column (85°C isotherm 20 min, 30°C/min to 220°C): tR (S) = 13.4 min, tR (R) = 17.9 min.
(S)-3-Methylcyclopentanone

Column chromatography (25% Et₂O in PE) afforded the product as a colorless oil. GC yield: 94%, isolated yield: 80% due to high volatility, 89% ee. [α]²⁰_D: −13.2 (c = 1.0, CHCl₃); ¹H NMR (200 MHz, CDCl₃) δ 3.22 – 2.70 (m, 1H), 2.51 – 1.81 (m, 5H), 1.32 – 1.29 (m, 1H), 1.11 – 1.02 (m, 3H). Determination of enantiomeric excess BGB175 column (85°C isotherm 20 min, 30°C/min to 220°C): t_R (S) = 8.1 min, t_R (R) = 8.5 min.

(S)-3-Phenylcyclohexanone

Column chromatography (25% Et₂O in light petrol) afforded the product as a colorless oil. GC yield: 86%, isolated yield: 84%, 82% ee. [α]²⁰_D: −17.2 (c = 1.0, CHCl₃); ¹H NMR (200 MHz, CDCl₃) δ 7.39 – 7.37 (m, 2H), 7.32 – 7.27 (m, 3H), 3.11 – 3.00 (m, 1H), 2.68 – 2.44 (m, 4H), 2.23 – 2.15 (m, 2H), 1.93 – 1.81 (m, 2H). Determination of the enantiomeric excess BGB175 column (120°C isotherm 55 min, 30°C/min to 220°C): t_R (S) = 48.8 min, t_R (S) = 49.5 min.

(S)-3-Phenethylcyclohexanone

Column chromatography (25% Et₂O in light petrol) afforded the product as a colorless oil. GC yield: 94%, isolated yield: 91%, 90% ee. ¹H NMR (200 MHz, CDCl₃) δ 7.37 – 7.22 (m, 5H), 2.75 – 2.33 (m, 5H), 2.14 – 1.70 (m, 7H), 1.49 – 1.38 (m, 1H). Determination of the enantiomeric excess Chiralcel Diacel AS-H column (n-heptane/i-PrOH 97/3 V/V%, 1 mL/min, 25°C, λ = 220 nm): t_R (R) = 15.6 min, t_R (S) = 16.6 min.

(S)-3-(Naphtalen-1-yl)cyclohexanone

Column chromatography (25% Et₂O in light petrol) afforded the product as a colorless oil. GC yield: 65%, isolated yield: 62%, 94% ee. [α]²⁰_D: −49.2 (c = 1.0, CHCl₃); ¹H NMR (200 MHz, CDCl₃) δ 8.05 – 7.75 (m, 3H), 7.54 – 7.38 (m, 4H), 3.92 – 3.82 (m, 1H), 2.75 – 1.94 (m, 8H). Determination of the enantiomeric excess Chiralcel Diacel AS-H column (n-heptane/i-PrOH 95/5 V/V%, 1 mL/min, 25°C, λ = 220 nm): t_R (R) = 13.8 min, t_R (S) = 22.7 min.
(S)-3-Piperonylcyclohexanone

Column chromatography (25% Et₂O in light petrol) afforded the product as a colorless oil. GC yield: 65%, isolated yield: 62%, 94% ee. [α]D20 = -15.3 (c = 1, CHCl₃);

$^1$H NMR (200 MHz, CDCl₃) δ 6.74 – 6.63 (m, 3H), 5.93 (s, 2H), 2.98 – 2.87 (m, 2H), 2.54 – 2.39 (m, 4H), 2.17 – 2.02 (m, 2H), 1.83 – 1.73 (m, 2H). Determination of enantiomeric excess Chiralcel Diacel AS-H column (n-heptane/i-PrOH 85/15 V/V%, 1 mL/min, 25°C, λ = 220 nm): tₗ (S) = 23.5 min, tₗ (R) = 28.0 min.
6.3 Optimization of reaction conditions

Table S1.: Proof of concept in 1,4-dioxane

| Entry | Counteranion | Yield [b] [%] | ee [c] [%] | Δee [d] [%] |
|-------|--------------|---------------|-----------|-----------|
| 1     | F₃C-O⁻      | 49            | 54 (S)    | -         |
| 2     | F₃C-O⁻      | 49            | 54 (S)    | -         |
| 3     | Ph₃P-O⁻     | 27            | 64 (S)    | +10       |
| 4e    | Ph₃P-O⁻     | 72            | 74 (S)    | +23       |
| 5     | rac-4       | 13            | 54 (S)    | 0         |
| 6     | (R)-8       | 13            | 54 (S)    | 0         |
| 7     | (S)-8       | 15            | 54 (S)    | 0         |

a Performed with 0.18 mmol 3-methyl-2-cyclohexenone, 0.036 mmol catalyst, 0.22 mmol Hantzsch ethyl ester in 0.55 mL 1,4-dioxane at 60°C for 48 hours. b Determined by GC analysis using n-dodecane as internal standard. c Determined by chiral GC analysis using a BGB175 chiral capillary column. Absolute configurations have been determined by measuring the optical rotation and comparing with literature data. d ee difference compare to the reaction with TFA counteranion. e MTBE was used as solvent.
Table S2.: Solvent screening

| Entry | Solvent     | Yield<a> [%] | ee<c> [%] |
|-------|-------------|--------------|-----------|
| 1     | EtOAc       | 48           | 67 (S)    |
| 2     | BuOAc       | 41           | 62 (S)    |
| 3     | THF         | 60           | 68 (S)    |
| 4     | 1,4-Dioxane | 27           | 64 (S)    |
| 5     | MTBE        | 72           | 74 (S)    |
| 6     | Bu2O        | 16           | 62 (S)    |
| 7     | Toluene     | 17           | 75 (S)    |
| 8     | CHCl3       | 23           | 53 (S)    |
| 9     | H2O         | 9            | 42 (S)    |
| 10    | MeOH        | 10           | 30 (S)    |
| 11    | EtOH        | 20           | 50 (S)    |
| 12    | 1PrOH       | 26           | 57 (S)    |
| 13    | 1BuOH       | 30           | 60 (S)    |
| 14    | Acetonitrile| 17           | 37 (S)    |

*a* Performed with 0.18 mmol 3-methyl-2-cyclohexenone, 0.036 mmol catalyst, 0.22 mmol Hantzsch ethyl ester in 0.55 mL solvent at 60°C for 48 hours. *b* Determined by GC analysis using *n*-dodecane as internal standard. *c* Determined by chiral GC analysis using a BGB175 chiral capillary column. Absolute configurations have been determined by measuring the optical rotation and comparing with literature data.
Table S3.: Phosphoric acid screening

| Entry | Phosphoric acid | Yieldb [%] | eec [%] |
|-------|----------------|------------|---------|
| 1     | ![Phosphoric acid 4](image) | 72 | 74 (S) |
| 2     | ![Phosphoric acid 5](image) | 70 | 77 (S) |
| 3     | ![Phosphoric acid 6](image) | 94 | 80 (S) |
| 4     | ![Phosphoric acid 7](image) | 43 | 76 (S) |

a Performed with 0.18 mmol 3-methyl-2-cyclohexenone, 0.036 mmol catalyst, 0.22 mmol Hantzsch ethyl ester in 0.55 mL MTBE at 60°C for 48 hours. b Determined by GC analysis using n-dodecane as internal standard. c Determined by chiral GC analysis using a BGB175 chiral capillary column. Absolute configurations have been determined by measuring the optical rotation and comparing with literature data.
Table S4.: Comparison of selectivity by screening other acids

![Chemical reaction diagram]

| Entry<sup>a</sup> | Acid | Yield<sup>b</sup> [%] | ee<sup>c</sup> [%] |
|-------------------|------|----------------------|------------------|
| 1                 | ![Acid 1](image) | 34                   | 58 (S)           |
| 2                 | ![Acid 2](image) | 91                   | 37 (S)           |
| 3                 | ![Acid 3](image) | 93                   | 45 (S)           |
| 4                 | ![Acid 4](image) | 45                   | 55 (S)           |
| 5                 | ![Acid 5](image) | 40                   | 52 (S)           |
| 6                 | ![Acid 6](image) | 88                   | 51 (S)           |
| 7                 | ![Acid 7](image) | 94                   | 80 (S)           |

<sup>a</sup> Performed with 0.18 mmol 3-methyl-2-cyclohexenone, 0.036 mmol catalyst, 0.22 mmol Hantzsch ethyl ester in 0.55 mL MTBE at 60°C for 48 hours.  
<sup>b</sup> Determined by GC analysis using n-dodecane as internal standard.  
<sup>c</sup> Determined by chiral GC analysis using a BGB175 chiral capillary column. Absolute configurations have been determined by measuring the optical rotation and comparing with literature data.
Table S5: L-Amino acid screening

| Entry<sup>a</sup> | L-amino acid | Yield<sup>b</sup> [%] | ee<sup>c</sup> [%] |
|-------------------|--------------|-----------------------|-----------------|
| 1                 | ![L-amino acid 1](image1) | 94                    | 80 (S)          |
| 2                 | ![L-amino acid 2](image2) | 52                    | 77 (S)          |
| 3                 | ![L-amino acid 3](image3) | 73                    | 72 (S)          |
| 4                 | ![L-amino acid 4](image4) | 55                    | 9 (S)           |
| 5                 | ![L-amino acid 5](image5) | 83                    | 60 (S)          |
| 6                 | ![L-amino acid 6](image6) | 91                    | 76 (S)          |
| 7                 | ![L-amino acid 7](image7) | 73                    | 33 (S)          |

<sup>a</sup> Performed with 0.18 mmol 3-methyl-2-cyclohexenone, 0.036 mmol catalyst, 0.22 mmol Hantzsch ethyl ester in 0.55 mL MTBE at 60°C for 48 hours.  
<sup>b</sup> Determined by GC analysis using n-dodecane as internal standard.  
<sup>c</sup> Determined by chiral GC analysis using a BGB175 chiral capillary column. Absolute configurations have been determined by measuring the optical rotation and comparing with literature data.
Table S6: Ester screening

| Entry | L-valine ester | Yield<sup>b</sup> [%] | ee<sup>c</sup> [%] |
|-------|----------------|------------------------|------------------|
| 1     | ![Structure](image1.png) | 94 | 80 (S) |
| 2     | ![Structure](image2.png) | 90 | 76 (S) |
| 3     | ![Structure](image3.png) | 70 | 57 (S) |
| 4     | ![Structure](image4.png) | 95 | 50 (S) |
| 5     | ![Structure](image5.png) | 92 | 74 (S) |
| 6     | ![Structure](image6.png) | 94 | 73 (S) |
| 7     | ![Structure](image7.png) | 98 | 85 (S) |
| 8     | ![Structure](image8.png) | 98 | 93 (S) |
| 9     | ![Structure](image9.png) | 98 | 82 (S) |

<sup>a</sup> Performed with 0.18 mmol 3-methyl-2-cyclohexenone, 0.036 mmol catalyst, 0.22 mmol Hantzsch ethyl ester in 0.55 mL MTBE at 60°C for 48 hours. <sup>b</sup> Determined by GC analysis using n-dodecane as internal standard. <sup>c</sup> Determined by chiral GC using a BGB175 chiral capillary column. Absolute configurations have been determined by measuring the optical rotation and comparing with literature data.
Table S7: Screening of catalyst loading and temperature

| Entry | Temperature | Catalyst loading [mol%] | Hantzsch ester | Yield [%] | ee [%] |
|-------|-------------|--------------------------|----------------|-----------|--------|
| 1     | 60          | 20                       | ethyl          | 98        | 93 (S) |
| 2     | 50          | 20                       | ethyl          | 98        | 95 (S) |
| 3     | 40          | 20                       | ethyl          | 96        | 95 (S) |
| 4     | 25          | 20                       | ethyl          | 59        | 96 (S) |
| 5     | 25          | 10                       | ethyl          | 43        | 96 (S) |
| 6     | 25          | 5                        | ethyl          | 29        | 96 (S) |
| 7     | 25          | 1                        | ethyl          | 11        | 96 (S) |
| 8     | 50          | 10                       | ethyl          | 99        | 94 (S) |
| 9     | 50          | 5                        | ethyl          | 98        | 95 (S) |
| 10    | 50          | 1                        | ethyl          | 68        | 93 (S) |
| 11<sup>d</sup> | 25         | 20                       | methyl         | 14        | 83 (S) |
| 12<sup>d</sup> | 25         | 20                       | ethyl          | 17        | 88 (S) |
| 13<sup>d</sup> | 25         | 20                       | i-propyl       | 58        | 69 (S) |
| 14<sup>d</sup> | 25         | 20                       | t-butyl        | 58        | 67 (S) |

<sup>a</sup> Performed with 0.18 mmol 3-methyl-2-cyclohexenone, 0.009-0.036 mmol catalyst, 0.22 mmol Hantzsch ester in 0.55 mL MTBE at the given temperature for 48 hours. <sup>b</sup> Determined by GC analysis using n-dodecane as internal standard. <sup>c</sup> Determined by chiral GC analysis using a BGB175 chiral capillary column. Absolute configurations have been determined by measuring the optical rotation and comparing with literature data. <sup>d</sup> Performed with (L)-valine t-butyl ester instead of (L)-valine (+)-(1R,3R,4S) menthyl ester.
### 6.4 Reaction scope and limitations

![Diagram of reaction](image)

| Entry | Substrate | Yield [\%] | ee [\%] |
|-------|-----------|-------------|---------|
| 1     | ![Substrate 1a](image) | 98 (72)\(^f\) | 95 (S)  |
| 2     | ![Substrate 1b](image) | 85 (76)\(^f\) | 92 (S)  |
| 3     | ![Substrate 1c](image) | 70 (55)\(^f\) | 91 (S)  |
| 4     | ![Substrate 1d](image) | 91 (87)     | 93 (S)  |
| 5     | ![Substrate 1e](image) | 85 (60)\(^f\) | 86 (S)  |
| 6     | ![Substrate 1f](image) | 75 (68)\(^f\) | 88 (S)  |
| 7\(^b\) | ![Substrate 1g](image) | 66 (60)     | 92 (S)  |
| 8\(^c\) | ![Substrate 1h](image) | 94 (80)\(^f\) | 89 (S)  |
| 9     | ![Substrate 1i](image) | 86 (84)     | 82 (S)  |
Performed with 1.8 mmol ketone, 5 mol% catalyst and 2.2 mmol Hantzsch ethyl ester in 5.5 mL MTBE at 50°C for 48 h. b 20 mol% catalyst. c 10 mol% catalyst. d Determined by GC or GC-MS analysis. Isolated yields after flash column chromatography are given in parenthesis. e Determined by chiral GC analysis using a BGB175 or BGB173 chiral capillary column, or by chiral HPLC analysis using a Diacel Chiralcel AS-H column. Absolute configurations have been determined by measuring the optical rotation and comparing with literature data. f Lower isolated yield because of high volatility of the product.
7. Computational studies

7.1 Quantummechanical calculation of rotational barriers

7.1.1 Choice of method and basis set

Although several studies on the calculation of rotational barriers in substituted biphenyls have been published, the only systematic protocol so far has been established by Masson. A key finding of Masson’s study is that for accurate barrier energies, inclusion of vibrational corrections is crucial. Since frequency computations as well as transition state optimizations for molecules as large as the substituted phosphoric acids can become quite expensive, a compromise between accuracy and efficiency is necessary in terms of the method.

The popular as well as efficient B3LYP functional has been shown to perform well for the estimation of rotational barriers for unsubstituted and substituted biphenyls. However, as also noted by Masson, empirical dispersion correction terms such as Grimme’s DFT-D or DFT-D3 are necessary to obtain accurate energies with B3LYP, so we chose B3LYP-D3 as a functional. The correlation of the uniform electron gas in the B3LYP functional was modeled according to the Vosko-Wilk-Nusair VWN5 formalism.

Since Masson achieved good results with DFT/def2-TZVPP, we tested both the single-polarized def2-TZVP and double-polarized def2-TZVPP set for compound 4. Since energies on the B3LYP-D3 level of theory differed only by 0.07 kcal/mol between both basis sets, we chose the computationally cheaper def2-TZVP basis set. Summarizing, all geometry optimizations, energy evaluations and frequency calculations (at 333.15K) were performed on the B3LYP-D3/def2-TZVP level of theory. All computations were performed with ORCA. For further validation of the method, we compared the B3LYP-D3/def2-TZVP electronic barrier energies of phosphoric acid 4 against single point electronic energies on the same geometry computed on the benchmark DLPNO-CCSD(T)/def2-QZVP level of theory. Only a small energy difference of 0.28 kcal/mol could be observed.

Masson also addresses the role of solvent when computing rotational barriers. In all studies on the computation of biphenyl racemization barriers published so far, good agreement with experiment is achieved without the consideration of solvent effects. Possible justification can be found in a study by Graybill and Leffler, who found a compensation of enthalpy and entropy in different solvents. For a more detailed discussion, see References 30 and 39.

However, Masson emphasizes that solvent effects cannot be confidently neglected for negatively charged biphenyls. Since solvent effects and likely specific interactions with both solvent and cation
need to be considered when computing rotational barriers of the anionic forms of phosphoric acids 4-7, the barrier of the corresponding anions will be the topic of more detailed future work.

7.1.2 Optimization of transition states

The systematic search for rotational transition states is not straightforward. Usually, fixing the torsional dihedral angle around the aryl-aryl bond to 0 degrees and optimizing this constrained structure yields good guesses for rotational transition states of substituted biphenyl.\textsuperscript{30} The situation is trickier when the planar transition state is hindered by bulky ortho-substituents such as the isopropyl and tert-butyl groups in phosphoric acids 6 and 7. For all phosphoric acids, we optimized the structure while fixing one of the dihedral angles to 0° and used the result as guesses for the transition state optimizations. In addition, for phosphoric acid 6 we performed a systematic transition state search with the nudged elastic band (NEB) method implemented in ORCA.\textsuperscript{40,41} We also used the result of this NEB calculation to construct another transition state guess for phosphoric acid 7. The imaginary frequencies of all transition states corresponded to an out-of-plane torsion of the phenyl rings. For phosphoric acids 4 and 5, fully planar transition states as depicted in Figure S1 are obtained when using the constrained structures as transition state guesses.

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{transition_states.png}
\caption{Rotational transition states for phosphoric acids 4 and 5.}
\end{figure}

As already mentioned, compounds 6 and 7 have methyl groups in the 6,6′-position, which hinder the planar transition state. Instead, they adopt a conformation in which the aryl-aryl-bond is out-of-plane and the two rings roughly coplanar. This peculiar transition state geometry for ortho-substituted biphenyls has been anticipated by Baddeley as early as 1946.\textsuperscript{42} Ling and Harris proposed the associated mechanism in 1964.\textsuperscript{43} They suggested an asynchronous nature of the racemization, with 6,6′-groups passing over each other subsequently instead of synchronously, minimizing the barrier energy. The out-of-plane transition states as well as the asynchronous nature of the racemization has been confirmed by Masson’s calculation.\textsuperscript{30} The asynchronous mechanism is also visible in the case of both phosphoric acids 6 and 7. By constraining different dihedral angles during pre-optimization, two different transition states can be obtained. The first transition state corresponds to passing of the methyl groups prior to
reaching the transition state, in the second transition state the ester oxygens of the phosphate groups have passed instead (Figure S2 and S3, left and right). No pathway is favored over the other, the electronic barriers of the two transition states for both phosphoric acid 6 and 7 only differ by 0.01 kcal/mol.

Figure S2: Asynchronous transition states for phosphoric acid 6.

Figure S3: Asynchronous transition states for phosphoric acid 7.

7.2 Molecular Dynamics Simulations

7.2.1 Simulation setup

Force fields for the anionic form of anion 6 and the iminium intermediate evolving from the L-valine (+)-(1S,2R,5S)-menthyl-cation were obtained from PARAMCHEM\textsuperscript{44,45} without further modification. Since no force field for MTBE was available, we chose n-methylbutylether as a solvent. The solvent parameters were taken from the CGenFF force field\textsuperscript{46}. Simulation boxes contained a single ion pair and 216 molecules of n-methylbutylether. To consider all possible isomers and stereoisomers, both the (E)- and (Z)-form of the cation as well as both anion enantiomers were considered, yielding four different systems (see Table S8.). 10 replica simulations of every system were conducted under the following conditions: All simulations were performed with the program package CHARMM\textsuperscript{47} Initial configurations were created with PACKMOL\textsuperscript{48} All simulations were conducted in the NpT ensemble
and employed the CHARMM CPT algorithm, the leapfrog integrator and the Hoover thermostat. A temperature of 330 K, a pressure of 1 atm and a non-bonded cutoff of 11 Å were used. Electrostatics were treated using the Particle Mesh Ewald method, with a grid size of approximately 1 Å, cubic splines of order 6 and a $K$ of 0.41 Å$^{-1}$. The SHAKE algorithm was employed to fix the length of bonds to hydrogens.

Boxes were first equilibrated for 2 ns using a timestep of 1 fs, followed by production simulations of at least 38 ns (see Table S8 for system details) under the same conditions. Coordinates were written to disk every 250 steps.

For trajectory analysis, the MDAnalysis library$^{49}$ as well as self-written python code was used. Plots were created with R (ggplot)$^{50}$ Hydrogen bonds were analyzed using CHARMM and a cutoff distance of 2.4 Å and a cutoff angle of 135°. Every 10th step of the trajectory was considered in the analysis.

### 7.2.2 Statistical considerations

To ensure statistical convergence of the simulations, several measures were taken. For both cation isomers (E and Z) 10 different conformers optimized for RMSD diversity were generated using a genetic algorithm implemented in OpenBabel.$^{51}$ Sampling of anion conformations was not done due to the structural rigidity of the anion. For each of the 10 replica/systems, a different cation conformer was used to create an initial configuration. Since we were especially interested in ion-ion-interactions, we monitored the distribution of several atom-atom interionic distances to assess sampling. Every system was simulated until the distributions reached convergence, the respective times for every system are listed in Table S8. These converged distributions are depicted in Figure S4 and show that especially the N23-O48 and N23-O49 distance distributions show full overlap.

To illustrate the distribution prior to convergence, the distributions of the E/S system after 38 ns and the full simulation time of 78 ns are depicted in Figure S5. It can be clearly seen that the N23-O48 and
N23-O49 distance distributions are different at 38 ns, but after a simulation time of 78 ns the distributions have equalized.

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**Figure S4.** Interionic distances illustrated for the E-cation/S-anion pair (top) and the distributions after the full simulation time (bottom). Simulation times for the different systems are listed in Table S8.
Figure S5. Distribution of interionic distances for the E-cation/S-anion pair after 38 ns (left) and 78 ns (right) simulation time. It is clearly visible that 78 ns are necessary to converge the distributions.
8. NMR spectra of L-amino acid derivatives
9. NMR spectra of phosphoric acids and its intermediates
10. NMR spectra of ATH substrates
11. NMR spectra of ATH products
12. Chiral GC and HPLC traces

![Chiral GC and HPLC traces]

**2a**
Racemic

**Peak Number** | **Area %** | **Ret. Time** | **Area** | **BC**
--- | --- | --- | --- | ---
1 | 50.3577 | 8.92 | 16956605 mi | 
2 | 49.6423 | 9.43 | 1679506 mi | 
**Totals** | **100.0000** | | **336217** | 

![Chiral GC and HPLC traces](image2)

**Peak Number** | **Area %** | **Ret. Time** | **Area** | **BC**
--- | --- | --- | --- | ---
1 | 97.0301 | 0.99 | 13073065 mi | 
2 | 2.1699 | 9.62 | 30711 mi | 
**Totals** | **100.0000** | | **1338017** | 

**2a**
Enantioenriched
| Peak Number | Area % | Ret. Time | Area | BC     |
|-------------|--------|-----------|------|--------|
| 1           | 58.6671| 49.31     | 219066 µl |
| 2           | 49.3323| 50.21     | 213263 µl |
| Totals      | 100.0000 |          | 432299    |

![Racemic](image1)

| Peak Number | Area % | Ret. Time | Area | BC     |
|-------------|--------|-----------|------|--------|
| 1           | 8.9984 | 48.78     | 149429 µl |
| 2           | 91.0016| 49.46     | 1511189 µl|
| Totals      | 100.0000 |          | 1660618    |

![Enantioenriched](image2)
### Integration Results

| No. | Peak Name | Retention Time (min) | Area (mAU*min) | Height (mAU) | Relative Area (%) | Relative Height (%) | Amount (n.a.) |
|-----|-----------|----------------------|----------------|--------------|-------------------|---------------------|---------------|
| 1   |           | 15.773               | 1,368          | 3.867        | 51.01             | 52.59               | n.a.          |
| 2   |           | 16.732               | 1,314          | 3.480        | 48.99             | 47.41               | n.a.          |
| **Total:** |          |                      | **2,682**      | **7,353**    | **100.00**        | **100.00**          |               |

**Peak #1** 100% at 15.77 min

**Peak #2** 100% at 18.73 min
### Integration Results

| No. | Peak Name | Retention Time (min) | Area (mAU/min) | Height (mAU) | Relative Area (%) | Relative Height (%) | Amount |
|-----|-----------|----------------------|----------------|--------------|------------------|---------------------|--------|
| 1   |           | 15.578               | 0.610          | 1.737        | 5.45             | 6.49                | n.a.   |
| 2   |           | 16.610               | 10.569         | 25.025       | 94.54            | 93.51               | n.a.   |
| **Total:** | | **11.179** | **26.762** | | **100.00** | **100.00** |        |

- **Peak #1** 100% at 15.56 min
  - %: 208.3
  - %: 260.1

- **Peak #2** 100% at 16.61 min
  - %: 207.0
  - %: 235.8
Integration Results

| No. | Peak Name | Retention Time (min) | Area (mAU*min) | Height (mAU) | Relative Area (%) | Relative Height (%) | Amount (n.a.) |
|-----|-----------|----------------------|----------------|--------------|------------------|---------------------|---------------|
| 1   |           | 23.583               | 26.752         | 21.686       | 84.92            | 87.25               | n.a.          |
| 2   |           | 28.123               | 4.573          | 3.168        | 15.08            | 12.75               | n.a.          |
| Total: |       |                      | 30.325         | 24.854       |                  |                     |               |

Peak #1 100% at 23.58 min

Peak #2 100% at 28.12 min
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