Supporting Information

General Procedure.

All laboratory scale reactions were performed in a dry nitrogen atmosphere using standard Schlenk techniques or in the glove box. Anhydrous solvents over molecular sieve purchased from Fluka were systematically used. Amines (generally > 99%) were used as provided by Aldrich, Fluka, Acros. Triethylamine was stored over KOH pellets. Normal binol, octahydrobinol and 3,3'-dimethylbinol based phosphorus chloride was prepared according to a published procedure.\textsuperscript{1} \textsuperscript{1}Rh(COD)\textsubscript{2}BF\textsubscript{4} was provided by Umicore and Heraeus. The hydrogenation substrate used in the laboratory scale experiment was obtained from Merck. The library was synthesized using a Zinsser Lissy liquid handling robot equipped with 4 probes and placed inside a glove box. Whatman PKP 2mL 96-well filter plates in combination with the UniVac 3 vacuum manifold were used to perform the parallel filtration of the ligand library. The hydrogenation reaction is carried out in a Premex 96-Multi Reactor\textsuperscript{2} that can accommodate 96 reactions vessels at the same temperature and hydrogen pressure or in the Endeavor\textsuperscript{TM3}.

Analytical method

HPLC-conditions:

Column: 2 x Lichrosphere DIOL 50 x 4.6 mm ID + Chiralpak AD 50 x 4.6 mm ID
Eluent A: n-heptane
Eluent B: ethanol

Gradient:

<table>
<thead>
<tr>
<th>time</th>
<th>n-heptane % v/v</th>
<th>ethanol % v/v</th>
<th>flow mL/min</th>
</tr>
</thead>
<tbody>
<tr>
<td>Min</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>96</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>16</td>
<td>96</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>16.1</td>
<td>75</td>
<td>25</td>
<td>2</td>
</tr>
<tr>
<td>18</td>
<td>75</td>
<td>25</td>
<td>2</td>
</tr>
</tbody>
</table>
Runtime: 23 min
Flow: 1 mL / min
Temperature: 25 °C
Injection volume: 1 µL
Detection: UV 220 nm

Starting material = 8.5min
Desired enantiomer = 11.9min
Undesired enantiomer = 13.3min

Synthesis of the library of ligands.

Stock solutions: Stock solutions were prepared by dissolving the proper amounts of every reagent necessary for the library synthesis in dry toluene. The following concentration were used:

- normal-binol-chlorophosphite, octhydrobinol-chlorophosphite, 3,3’-dimethylbinol-chlorophosphite: 0.15M
- amines: 0.158M
- Et3N: 0.536M
**Ligand Synthesis:** For each of the 96 ligands, 0.333mL of the chlorophosphite solution was transferred into a well of the Whatman PKP 96 wells filter plate. 0.1mL of the triethylamine and 0.333mL of the amine solution were added (see Table 1). The microtiter plate was placed on an orbital shaker and vortexed for 2 hours. The microtiter plate was then placed onto the vacuum manifold and filtration was performed upon application of the vacuum. The filtrates, i.e. 96 solutions of different phosphoramidites (0.766mL, concentration=0.065M) were collected and stored into a 96-well polypropylene microplate.

<table>
<thead>
<tr>
<th>V (mL)</th>
<th>mMol</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCl 0.333</td>
<td>0.0499</td>
<td>1</td>
</tr>
<tr>
<td>Et3N 0.1</td>
<td>0.0505</td>
<td>1.01</td>
</tr>
<tr>
<td>R1R2NH 0.333</td>
<td>0.0508</td>
<td>1.02</td>
</tr>
</tbody>
</table>

**Table 1.** Volume of stock solutions used in the synthesis of the 32 ligands.

**Preparation of the catalytic mixture:** A stock solution of the Rh precursor, Rh(COD)\(_2\)BF\(_4\) was prepared in dry dichloromethane ([Rh]=0.0131M) as well as stock solutions for the enamide with a concentration of 0.073M in EtOH.

<table>
<thead>
<tr>
<th>Conc. [M]</th>
<th>Volume (mL)</th>
<th>mMol</th>
<th>Ratio rel. to Rh</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rh 0.0131</td>
<td>0.25</td>
<td>0.0033</td>
<td>1</td>
</tr>
<tr>
<td>Ligand 0.0651</td>
<td>0.1</td>
<td>0.0065</td>
<td>1.98</td>
</tr>
<tr>
<td>Substrate 0.073</td>
<td>2.25</td>
<td>0.164</td>
<td>50</td>
</tr>
</tbody>
</table>

**Table 2.** Volume of stock solutions used in the preparation of the reaction mixture.

The proper amount of the 96 ligand solutions was transferred from the microtiter plate into 96 5mL vials, equipped with stir bars. The toluene was left to evaporate. The Rh stock solution was then added to each of the vials allowing the formation of 96 different catalysts. The hydrogenation substrate was then added. (ratio Rh/ligand=2, ratio substrate/ligand=50, [Rh]=0.0013M).

**Hydrogenation:** The catalytic mixtures were transferred under inert atmosphere to the parallel hydrogenation reactor. The vials were pressurized/depressurized 5 times with 10 bars of N\(_2\), followed by 5 times with 10 bars of hydrogen and put under a pressure of 25 bars of H\(_2\). The reactions were left stirring at room temperature for 3 hours. The mixtures were then analyzed by
chiral HPLC to determine the conversion and the e.e. Absolute configuration was determined by comparison with reference compound.

**Synthesis of G2, (R)-3,3’-dimethylbinaphyl-t-butoxy-phosphite.**

Stock solutions of the different reagents are prepared as follow: 1.577g of PCl$_3$ (11.5 mmol) is dissolved in 10 mL of dry toluene. 0.847g of $t$-butanol (11.5 mmol) is dissolved in 10 mL of dry toluene. 1.23 of Et$_3$N (12.2 mmol) is dissolved in 10 mL of dry toluene. The stock solutions are brought in the glove box. The solutions of $t$-butanol and Et$_3$N are mixed together and added slowly to the solution of PCl$_3$. The reaction mixture is left to stir for 1h. 3.614g of (R)-3,3’-dimethylbinol (11.5 mmol) is dissolved in 5 mL of dry toluene, together with 2.308g of Et$_3$N (22.85 mmol). The binol solution is slowly added to the reaction mixture and left to stir for 45 min. The reaction mixture is then filtered on a glass frit (P4), the left-over solid are washed with 2x15mL dry toluene. The filtrates are split in two batches. One batch is kept in the glove box. The other is taken out of the glove box to the vacuum line where the solvent is evaporated under vacuum from around 50mL to about 5mL. 20mL of pentane is added to the solution, yielding a small amount of precipitate, which is filtered off. The filtrate is collected and the solvent is evaporated under vacuum, yielding a white sticky solid. $^1$H NMR (Toluene d-8) $\delta$: 7.88-7.11 (m, 10H), 2.85 (s, 3H), 2.77 (s, 3H), 1.54 (s, 9H); $^{31}$P NMR $\delta$: 155.5

**Synthesis of (COD)Rh(G2)$_2$BF$_4$.**

In the glovebox, Rh(COD)$_2$BF$_4$ (2.69g, 6.62mmol) is dissolved into 25mL of dry DCM. The phosphite G2 (6.04g, 14.5mmol, 2.2 eq/Rh) dissolved in 25mL of dry DCM is added dropwise to the Rh solution over a period of 30min. The dark red solution turns bright orange after addition of all the ligand. The mixture is stirred for 2h extra and heptanes is added leading to the precipitation of an orange solid (5.99g, Yield = 80%).

**Hydrogenation of enamide 3 in a 150mL autoclave.**

23mg of Rh(COD)(G2)$_2$BF$_4$ (0.02mmol) is placed in a Schlenk tube under N$_2$ and dissolved in 4mL of dry degassed DCM. A 150mL Parr autoclave is loaded with 3.98g of enamide 3 (10.5mmol). The autoclave is closed and purged with N$_2$. 50mL of dry degassed EtOAc is added. The mixture is stirred for a few minute prior to the addition of Rh catalyst solution (S/C = 530). The autoclave is purged with N2 and H2 filling/emptying cycles. The reactor is pressurized with 5 bar of H$_2$ and heated to 50C.
Once this temperature is reached, the reaction is stirred at 700rpm. The hydrogenation is stopped after 17h and analysis is performed using chiral HPLC. Conversion = 100%, e.e. 97.1%.

*Hydrogenation of the enamide 3 on 16-ltr scale:*

522g of enamide 3 (purity: 87.4%; 456g; 1.20mol) is added to the 16-ltr Pfaudler autoclave. 5780g of IPA (technical) is added and the stirring is started at 50rmp. The preformed catalyst (Rh(COD)(G2)2BF4; L=(R)-O,O’-(3,3’–Dimethyl-1,1’-Dinaphthyl-2,2’-diyl)-O-t-butyl-phosphite; 3.09g; 0.0027mol; 0.23mol%) dissolved in 100g of IPA is added to the autoclave. The autoclave is placed under inert atmosphere via 3 vacuum/N2 cycles, then evacuated one last time before being filled with 6 bars of H2. The stirrer is set to 600RPM and the oil heating mantel to 30°C. The temperature of the reaction mixture is measured to be 32°C. Conversion after 2.5h = 19%. An extra amount of catalyst (1.7g; 0.0015mol; 0.35mol% for total amount of catalyst) is added. Conversion after 21h = 99.9%. Analysis: yield = 90%, e.e=87%.

The same procedure is repeated for a second batch: 520g of enamide (purity: 87.4%; 454g) + 16g of pure enamide from small scale experiments; 5650g of IPA (technical); Initial amount of catalyst = 3.09g, 1.75g added after 2.5h (total = 0.35mol%). The conversion is 25% after 2.5h and 99.9% after 21h. Analysis: yield = 89%, e.e.=89%.

*Removal of N-Boc protecting group of the chiral amide 4 and preparation of the corresponding HCl salt:*

Under inert atmosphere, 415g of activated charcoal (Ecosorb C941) as a slurry in 1.3L of IPA was added to 827g of amide 4 (2.172mol, 89% e.e.) in 16.7L of IPA. The mixture was stirred for 5h at 40°C. After cooling down at 20°C, the mixture was filtered over dicalite and concentrated to 0.23Kg/L. 1.13L of 5N HCl in IPA was added and the reaction mixture was warmed up to 50°C. After 30min stirring, the solution was seeded with 9g of product and aged for 6h. After cooling down at 20°C, 311g of imidazole was added and the reaction mixture was stirred for 12h at 20°C. The solid were isolated by filtration, washed 4 times with 1.3L of IPA, and dried for 48h at 26°C under reduced
pressure (50mBar). 641g of solide is obtained: purity=92.1%w, yield=85.7%, e.e.=98.9%, Rh=83ppm.

Rework of the HCl salt of the deprotected amide:

557g of amide 4-HCl salt (1.768mmol, 98.9% e.e.) is placed into the reactor and under inert atmosphere. 5.19L of EtOH (4% H2O) is added and the solution is warmed up to 50°C. 290g of activated charcoal (Ecosorb C941) is added as a slurry in 1.1L of EtOH. The mixture is stirred for 1h ½ and filtered over Dicalite. The solids are washed twice with 1.245L of EtOH. The filtrates are placed on the rotovap and the volume is reduced to 1.9L. The solution is warmed up to 65°C and 3.5L of CH3CN is added. Upon cooling down, crystals start to form. The slurry is left stirring at slow speed (85rpm) overnight. The slurry is rotovaped down to 1.9L, warmed up to 65°C, and 5.43L of CH3CN is added. After cooling down to 20°C, the slurry is filter and the solids are washed twice with 0.625L of CH3CN and dried under vacuum (70mbar) at 50°C for 1 day: 519g (purity = 99.6% area, 97.3%w, e.e.=99.9%, Rh=3ppm).

2 This reactor was developed by Premex in cooperation with DSM. See: www.premex-reactorag.ch/e/spezialloesungen/produkteneuheiten/