Supporting Information

Instant Ligand Libraries. Parallel Synthesis of Monodentate Phosphoramidites and in-situ Screening in Asymmetric Hydrogenation

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General Procedure.

All 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. (R)-O,O’-(1,1’-Dinaphthyl-2,2’-diyl)-phosphorus chloride was prepared according to a published procedure.1 Rh(COD)2BF4 was provided by OMG. The hydrogenation substrates, N-acetyl-dehydrophenylalanine methyl ester (1) and 3-acetylamino-but-2-enoic acid methyl ester (2) were synthesized following published procedures.2

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 Reactor3 that can accommodate 96 reactions vessels at the same temperature and hydrogen pressure or in the Endeavor™4.

31P NMR spectra were recorded at room temperature in dry undeuterated toluene on a Bruker Avance 300 (300MHz).

Conversion and enantiomeric excesses were determined by capillary GC analysis with a CP-Chirasil-L-Val (25m, 0.25mm, 0.12µm, 175°C) for reaction with substrate (1) and a CP-Chirasil-Dex-CB column (25m, 0.25mm, 0.25µm, 140°C) for reaction with substrate (2).
Library Synthesis and Screening in Hydrogenation of (1) and (2).

Stock solutions: Stock solutions were prepared by dissolving the proper amounts of every reagent necessary for the library synthesis in dry toluene (see Table 1).

Table 1. Reagents used to prepare the library, CAS number and concentration of the stock solution in toluene.

<table>
<thead>
<tr>
<th>#</th>
<th>Position</th>
<th>Name</th>
<th>CAS #</th>
<th>Conc. [M]</th>
</tr>
</thead>
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<td></td>
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<td>(R)-O,O’-(1,1’-Dinaphtyl-2,2’-diyl)-phosphorus chloride</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>Triethylamine</td>
<td></td>
<td>0.505</td>
</tr>
<tr>
<td>1</td>
<td>1A</td>
<td>Butylamine</td>
<td>109-73-9</td>
<td>0.152</td>
</tr>
<tr>
<td>2</td>
<td>1B</td>
<td>Isopropylamine</td>
<td>75-31-0</td>
<td>0.145</td>
</tr>
<tr>
<td>3</td>
<td>1C</td>
<td>Ter-butylamine</td>
<td>75-64-9</td>
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</tr>
<tr>
<td>4</td>
<td>1D</td>
<td>3,3-dimethylbutylamine</td>
<td>15673-00-4</td>
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</tr>
<tr>
<td>5</td>
<td>2A</td>
<td>a-Nonylamine</td>
<td>112-20-9</td>
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</tr>
<tr>
<td>6</td>
<td>2B</td>
<td>Cyclohexylamine</td>
<td>108-91-8</td>
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<tr>
<td>7</td>
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<td>15</td>
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<td>5D</td>
<td>2-methoxyethylamine</td>
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<td>21</td>
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<td>Aminoacetaldehyde, dimethyl acetal</td>
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<tr>
<td>22</td>
<td>6B</td>
<td>N,N-diethylethylenediamine</td>
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<td>6C</td>
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<tr>
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<td>7A</td>
<td>Diethylamine</td>
<td>2771-79-1</td>
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<td>26</td>
<td>7B</td>
<td>Piperidine</td>
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<td>0.157</td>
</tr>
<tr>
<td>27</td>
<td>7C</td>
<td>N-methyl-tertbutylamine</td>
<td>86-74-8</td>
<td>0.159</td>
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<td>28</td>
<td>7D</td>
<td>(S)-(-)-1-methylbenzylamine</td>
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<td>0.150</td>
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<tr>
<td>29</td>
<td>8A</td>
<td>Methyl isonipecotate</td>
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<td>0.158</td>
</tr>
<tr>
<td>30</td>
<td>8B</td>
<td>e-caprolactam</td>
<td></td>
<td>0.161</td>
</tr>
<tr>
<td>31</td>
<td>8C</td>
<td>Carbazole</td>
<td></td>
<td>0.157</td>
</tr>
<tr>
<td>32</td>
<td>8D</td>
<td>Heptanmethylenimine</td>
<td></td>
<td>0.150</td>
</tr>
</tbody>
</table>
**Ligand Synthesis**: 0.333mL of the chlorophosphite solution was transferred into 32 wells of the Whatman PKP filter plate. 0.1mL of the triethylamine solution was added to each well. 0.333mL of each of the 32 amines solution was added to each of the 32 vials (see Table 2). The microplate was placed on an orbital shaker and vortexed for 2 hours. The microplate was then placed onto the vacuum manifold and filtration was performed upon application of the vacuum. The filtrates, i.e. 32 solutions of different phosphoramidites (0.766mL, concentration=0.065M) were collected and stored into a 96-well polypropylene microplate.

**Table 2. Volume of stock solutions used in the synthesis of the 32 ligands.**

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

**31P NMR analysis**: The 31P NMR spectra of library members # 3A, 1B, 4B, 7B, 4C, 6C, 6D, 7D were recorded in undeuterated toluene. No reference was used. In parenthesis, the relative areas of the peaks are given.

31P-NMR (121MHz, 8H-toluene) of 3A: δ 148.1 (89), 141.9 (4), 136.5 (7). 1B: δ 152.1 (74), 142 (12), 136.6 (14). 4B: δ 141.9, 136.5 (maj), 132.1, 32.6 (maj), 30.7, 28.9, 28.3, 26.7, 26. 7B: δ 145.9 (89), 142 (4), 136.6 (7). 4C: δ 151.1 (87), 142 (3), 136.6 (7), 33.1 (3). 6C: δ 136.5 (50), 33.3 (50). 6D: δ 145.8 (86), 141.9 (1), 136.5 (13). 7D: δ 152.4 (85), 141.9 (6), 136.5 (9).

Based on the literature, the peak at 136.5ppm can be attributed to the bis(1,1’-binaphthyl-2,2’-ene)-pyrophosphite.

**Preparation of the catalytic mixture**: A stock solution of the Rh precursor, Rh(COD)₂BF₄ was prepared in dry dichloromethane ([Rh]=0.0131M) as well as stock solutions for the two hydrogenation substrates with a concentration of 0.073M ((1) in dichloromethane, (2) in dry isopropanol).
**Table 3.** Volume of stock solutions used in the preparation of the reaction mixture.

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

The proper amount (see table 3) of the 32 ligand solutions was transferred from the microplate into two sets of 32 vials, equipped with stir bars. The toluene was left to evaporate overnight, as it was observed to have a negative effect on the catalyst. The Rh stock solution was then added to each of the 64 vials allowing the formation of two sets of 32 different catalysts. Solutions of the two substrates were then added respectively to each set, thus generating 64 catalytic mixtures, ready for hydrogenation (ratio Rh/ligand=2, ratio substrate/ligand=50, [Rh]=0.0015M).

*Hydrogenation:* The catalytic mixtures were transferred under inert atmosphere to the parallel hydrogenation reactor. The vials were purged with hydrogen and put under a pressure of 6 bars. The reactions were left stirring at room temperature for an hour. The mixtures were then analyzed by chiral GC to determine the conversion and the e.e.. Absolute configuration was determined by comparison with reference compound.
Results

Table 4. Conversion obtained during the hydrogenation of (1) and (2) with the library of ligands.

<table>
<thead>
<tr>
<th>#</th>
<th>Position</th>
<th>Substrate (1)</th>
<th>Substrate (2)</th>
<th>Substrate (2)</th>
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<td></td>
<td></td>
<td>Conv (%)</td>
<td>e.e. of S (%)</td>
<td>Conv (%)</td>
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<td>1A</td>
<td>100</td>
<td>78</td>
<td>29</td>
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<td>2</td>
<td>1B</td>
<td>100</td>
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<td>95</td>
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<td>100</td>
<td>80</td>
<td>99</td>
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<tr>
<td>8</td>
<td>2D</td>
<td>100</td>
<td>73</td>
<td>14</td>
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<tr>
<td>9</td>
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<td>100</td>
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<td>10</td>
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<td>11</td>
<td>3C</td>
<td>100</td>
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<td>12</td>
<td>3D</td>
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<td>4A</td>
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<td>14</td>
<td>4B</td>
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<tr>
<td>15</td>
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<td>32</td>
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</tbody>
</table>

Large-scale preparation of (R)-O,O’-(1,1’-Dinaphthyl-2,2’-diyl)-N-i-propylphosphorus amidite (LIB)

![Chemical structure](image_url)
In the glove box, 587 mg of O,O’-(1,1’-Dinaphthyl-2,2’-diyl)-phosphorus chloride (1.68 mmol) was placed in a vial and dissolved in 2 mL of dry toluene. 3.15 mL of a 0.559 M solution of diethylamine in toluene (1.76 mmol) and 3.49 mL of a 0.504 M solution of i-propylamine in toluene (1.76 mmol) were successively added to the chlorophosphite solution. After stirring for 2 hours, the reaction mixture was filtered through a glass frit and the solids were washed with 10 mL of toluene. The filtrates were collected and the solvent was removed under vacuum. The leftover solids were dissolved in 5mL toluene and purified with a SiO₂ column, previously treated with 1% solution of Et₃N in toluene. After evaporation of the solvent, 387 mg of a white solid (1.04 mmol, 62% yield) was obtained. ¹H NMR (Toluene d-8) δ: 7.63 (m, 4H), 7.42 (m, 4H), 7.05 (m, 4H), 3.24 (m, 1H), 2.55 (t, J=8.6 Hz, 1H), 0.85 (dd, J=20.3, 6.3Hz, 6H); ¹³C NMR δ: 26.33 (d, J=4.6 Hz, CH₃), 27.10 (d, J=3.5 Hz, CH₃), 43.48 (d, J=20.7 Hz, CH), 122.62 (d), 123.32 (d), 124.54/124.57 (s), 125/125.08 (s), 125.27 (d), 126.75 (d), 126.8 (d), 127.68 (d), 127.73 (d), 128.93 (d), 129.07 (d), 129.98 (d), 130.97 (d), 131.78 (s), 132.25 (s), 133.79 (s), 133.85 (s), 149.11/149.17 (s), 150.71 (s); ³¹P NMR δ: 152.2

**Hydrogenation with purified ligand:**

Several members of the library based on amines 7A, 1B, 7B, and 7D already prepared via the conventional procedure were used in hydrogenation of the two substrates for comparison purposes. For each ligands, the catalyst was preformed by mixing 8.1 mg of the Rh precursor, Rh(COD)₂BF₄ (2 mmol) with two equivalents of the ligand in 1 mL of dry DCM, under inert atmosphere. The reaction mixture was stirred for two hours and 0.5 mL of each of the 4 reaction mixtures was transferred twice into two different vessels of the Endeavor apparatus, thus filling the eight available vessels. The reactors were then purged with 5 low pressure/high pressure N₂ cycles. 5 mL of a 0.202 M stock solution of (1) in dry DCM was added to each of the first four vessels. 5 mL of a 0.2 M stock solution of (2) in dry isopropanol was added to each of the remaining four vessels (cf. Table 5). 5 low pressure/high pressure H₂ cycles were applied to the reactors. The H₂ pressure was then set at 5 bars and the reaction mixtures were stirred at 500 rpm. The hydrogen uptake was monitored during the course of the reaction. After 30 minutes, the reactors were opened and samples were taken and subjected after dilution to conversion and e.e. determination by GC (cf. Table 6).
Table 5. Endeavour Layout

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<th>Vessels</th>
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<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
</tr>
</thead>
<tbody>
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<td>Rh(COD)$_2$BF$_4$</td>
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<td>2 mmol</td>
<td>2 mmol</td>
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<td>2 mmol</td>
<td>2 mmol</td>
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</tr>
<tr>
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<td>7B</td>
<td>7D</td>
<td>1B</td>
<td>7A</td>
<td>7B</td>
<td>7D</td>
<td>1B</td>
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<td>(1)</td>
<td>(1)</td>
<td>(2)</td>
<td>(2)</td>
<td>(2)</td>
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</tr>
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Table 6. Results of the Endeavour run and comparisons with the results obtained with the same ligands in the library.

<table>
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<th>Vessel</th>
<th>Ligand</th>
<th>L Ref.</th>
<th>Sub</th>
<th>Endevour</th>
<th>Library</th>
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<td></td>
<td></td>
<td></td>
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<td>e.e. of S (%)</td>
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<td>100</td>
<td>73</td>
</tr>
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<td>NHiPr</td>
<td>B1</td>
<td>(1)</td>
<td>100</td>
<td>81</td>
</tr>
<tr>
<td>5</td>
<td>NEt2</td>
<td>A7</td>
<td>(2)</td>
<td>8</td>
<td>46</td>
</tr>
<tr>
<td>6</td>
<td>Piperidyl</td>
<td>B7</td>
<td>(2)</td>
<td>11</td>
<td>55</td>
</tr>
<tr>
<td>7</td>
<td>NHMeBenz</td>
<td>D7</td>
<td>(2)</td>
<td>96</td>
<td>94</td>
</tr>
<tr>
<td>8</td>
<td>NHiPr</td>
<td>B1</td>
<td>(2)</td>
<td>100</td>
<td>95</td>
</tr>
</tbody>
</table>

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