Supplemental Material with:

UREAphos: Supramolecular Bidentate Ligands for Asymmetric Hydrogenation

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Synthesis of ligand modules:

General phosphite preparation method:
1 mmol of alcohol, pre-dried by a co-evaporation procedure with toluene (three times), was dissolved in 10 ml of THF and 1 ml of Et_3N and cooled to 0°C. 1 mmol of bisnaphthol-PCl was added drops wise to the mixture. The resulting suspension was allowed to warm up to room temperature and stirred for 18 hours. The resulting white suspension was filtrated over celite and the filtrate was dried in *vacuo*. Purification was precipitation, accomplished by dissolving in 5 ml of toluene and subsequent addition of 5 ml of hexane, complemented if required by purification over a short plug of silica. Exceptions and details are listed below.

All ligands were prepared in two steps:

Synthesis of the ligands **B**, **C** and **D**
1) Synthesis of the urea-alcohol
To a solution of 10 mmol of the aminoalcohol dissolved in 10 ml of dichloromethane was added 10 mmol of the appropriate isocyanate. The products precipitate immediately upon forming as white solids and were obtained in pure form after filtration and washing with dichloromethane.

2) Synthesis of the ligands **B**, **C** and **D**
To a pre-dried mixture of 0.5 mmol of the ureum-alcohol (see step 1) and 500 mg of Amberlyst in 15 ml of THF at 0°C was added 0.5 mmol BisnaphtholPCl dissolved in THF. The resulting mixtures were stirred for 1 hour at this temperature and subsequently stirred for 18 hours at room temperature. The resulting mixtures were filtered, and the products were obtained pure as solid foams.

B
Yield: 34%. Tacky solid foam. ^{1}H NMR (300 MHz, $CDCl_3$) d 0.9 (t, 3H, CH_3), 1.2 (m, 2H, CH_3-C<u>H</u>$_2$), 1.3 (m, 2H, CH_3-CH_2-C<u>H</u>$_2$), 1.8 (m, 2H, C<u>H</u>$_2$-CH_2O), 2.9 (m, 2H, CH_2-NH), 3.3 (m, 2H, C<u>H</u>$_2$-CH_2-CH_2O), 4.1 (m, 2H, CH_2O), 4.5 (m, 1H, NH), 7.2-7.5 (m, 7H, ArH), 7.9-8.0 (m, 5H, ArH). ^{31}P NMR (121.4 MHz, $CDCl_3$, versus H_3PO_4) d141.2.

C
Yield: 43%. Solid foam. ^{1}H NMR (300 MHz, $CDCl_3$) d 1.4 (s, 6H, 2xCH_3), 3.9 and 4.1 (ab-pattern, 2H, CH_2), 4.8 (s, 1H, NH), 7.1 (m, 2H, ArH), 7.2-7.5 (m, 11H, ArH), 7.9-8.0 (m, 4H, ArH). ^{31}P NMR (121.4 MHz, $CDCl_3$, versus H_3PO_4) d144.6.

D
Yield: 43%. Solid foam. ^{1}H NMR (300 MHz, $CDCl_3$) d 0.9 (t, 3H, CH_3), 1.6 (m, 2H, CH_3-C$\underline{H}_2$), 3.9 (m, 2H, CH_2O), 4.1 (m, 1H, CH), 4.8 (d, 1H, NH), 6.3 (s, 1H, NH), 7.1 (m, 2H, ArH), 7.2-7.5 (m, 11H, ArH), 7.9-8.0 (m, 4H, ArH). ^{31}P NMR (121.4 MHz, $CDCl_3$, versus H_3PO_4) d143.8.

Synthesis of Ligand **E**
1) Preparation of 1-((1R,2S)-1-hydroxy-1-phenylpropan-2-yl)-3-(3-methoxyphenyl)urea: To a solution of 10 mmol of ephedrine in 10 ml of dichloromethane was added 10 mmol of 3-methoxyphenylisocyanate. The product precipitated as a white solid after several minutes and was obtained pure after filtration and washing with dichloromethane.Yield: 100%. White solid. ^{1}H NMR (500 MHz, DMSO-D6) d 0.9 (d, 3H, CH_3), 3.7 (s, 3H, CH_3), 3.9 (m, 1H, CHN), 4.7 (br, 1H, CHO), 5.5 (d, 1H, OH), 6.2 (d, 1H, NH), 6.5 (d, 1H, ArH), 6.8 (d, 1H, ArH), 7.1 (tr, 1H, ArH), 7.2 (s, 1H, ArH), 7.24 (m, 1H, ArH), 7.4 (m, 4H, ArH), 8.6 (s, 1H, NH).

2) Phosphite synthesis was performed according to the general procedure above described. Yield: 55%. ^{1}H NMR (500 MHz, $CDCl_3$) d 1.0 (d, 3H, CH_3), 3.7 (s, 3H, CH_3O), 4.2 (m, 1H, CHN), 5.0 (d, 1H, NH), 5.5 (d, 1H, CHO), 6.3 (s, 1H, NH), 6.6 (d, 1H, ArH), 6.7 (d, 1H, ArH), 6.8 (d, 1H, ArH), 6.9 (s, 1H, ArH), 7.5-7.1 (m, 13H, ArH), 7.6 (d, 1H, ArH), 8.0-7.8 (m, 3H, ArH). ^{31}P NMR (121.4 MHz, $CDCl_3$) d 141.5.

Synthesis of Ligand **F**
1) 1-(1R,2S)-(-)-2-hydroxy-1-methyl-2-phenylethyl-3-phenyl)thiourea was prepared analogous to 1-((1R,2S)-1-hydroxy-1-phenylpropan-2-yl)-3-(3-methoxyphenyl)urea.

2) Phosphite synthesis was performed according to the general procedure above described. Yield: 40%. White solid. ^{1}H NMR (300 MHz, $CDCl_3$) d 0.9 (d, 3H, J = 7.2 Hz, CH_3), 4.8 (m, 1H, CH), 5.9 (d, 1H, J = 9.9 Hz, CH), 6.3 (d, 1H, J = 5.7 Hz, NH), 7.1-7.5 (m, 19H, ArH), 7.7 (s, 1H, NH), 7.9-8.0 (m, 3H, ArH). ^{31}P NMR (121.4 MHz, $CDCl_3$, versus H_3PO_4) d 153.6.

Synthesis of Ligand **G**
1) Preparation of (R)-N-(1-hydroxybutan-2-yl)-1H-indole-2-carboxamide:
To a suspension of 6 mmol indole-2-carboxylic acid and 7 mmol of Et_3N in 20 ml of toluene, 6 mmol of DPPA was slowly added. The resulting yellowish suspension was stirred for 1 h at 80°C. At this temperature 6 mmol of 2-aminobutanol was added to the clear orange solution. This mixture was further stirred at room temperature for 18 hours. The resulting deep purple mixture was subsequently extracted from EtOAc using 2M HCl, $NaHCO_3$ and water. The organic phase was dried using $MgSO_4$ and the solvents were removed under reduced pressure. The purple solid crude product was purified using column chromatography (silica, 30% EtOAc in hexane gradually changing to EtOAc). The pure product was obtained as a purple solid.

2) Preparation of the Phosphite ligand **G**:

1 mmol of the alcohol, pre-dried by a co-evaporation procedure with toluene (three times), was dissolved in 10 ml of THF and 1 ml of Et_3N and cooled to -78°C. 1 mmol of -PCl was added drops wise to the mixture. The resulting suspension was allowed to warm up to room temperature and stirred for 18 hours. The light yellow suspension was filtrated over celite and the filtrate was dried in *vacuo*. Purification was performed on a short silica column eluting with dichloromethane and subsequently with EtOAc. Product was obtained as a white solid foam. Yield: 54%. White solid foam. ^{1}H NMR (300 MHz, $CDCl_3$) d 0.9 (tr, 3H, *J* = 7.5 Hz, CH_3), 1.6 (m, 2H, CH_3-C<u>H</u>$_2$), 3.9 (m, 1H, CH_2-C<u>H</u>-CH_2), 4.1 (m, 2H, CH_2O), 6.4 (d, 1H, *J* = 9.3 Hz, NH), 6.9 (s, 1H, CH=C(N)(N)), 7.1-7.4 (m, 12H, ArH), 7.6 (d, 1H, *J* = 7.5 Hz, NH), 7.9-8.0 (m, 4H, ArH), 9.3 (s, 1H, NH). ^{31}P NMR (121.4 MHz, $CDCl_3$, versus H_3PO_4) d141.6.

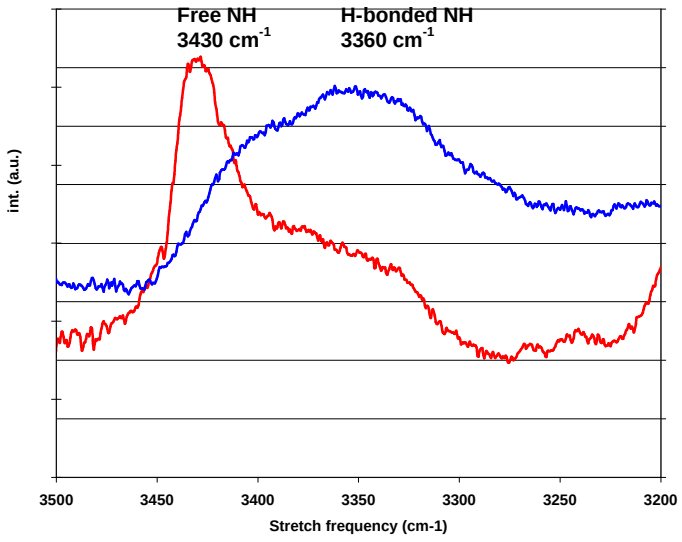
<u>Procedure for the binding studies (NMR and IR)</u>

This experiment was performed on a Thermo, Nicolet Nexus 670 FT-IR apparatus and a Varian Inova 500 NMR spectrophotometer. Dry, distilled $CDCl_3$ was used as the solvent.

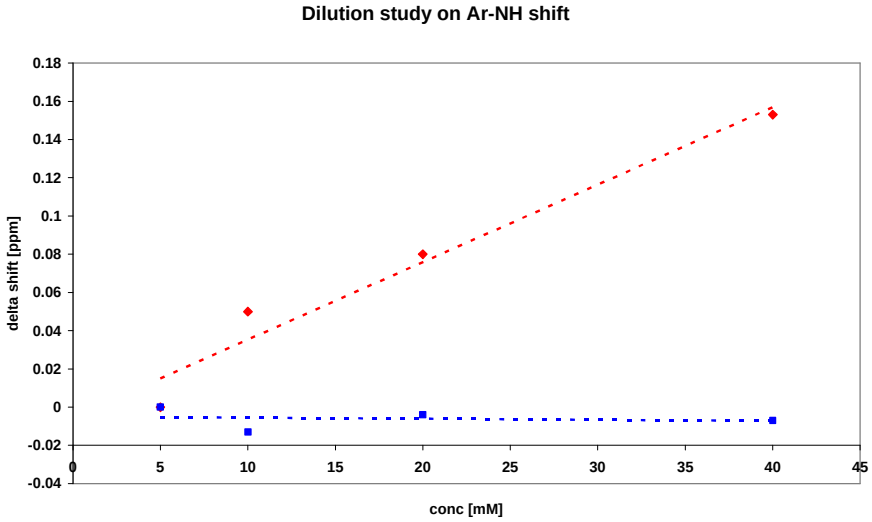
A series of solutions were prepared containing a 40 mM, 20 mM, 10 mM and 5 mM solution of [Rh(**D**)$_2$(NBD)](BF$_4$) in $CDCl_3$ respectively. This was performed by simply dissolving a 2 to 1 mixture of **D** and [Rh(NDB)$_2$](BF$_4$) in $CDCl_3$. The ^{1}H NMR spectra of these samples were recorded and also the IR spectra of the most diluted solution (5 mM). In a similar way a series of free ligand **D** containing 40 mM, 20 mM, 10mM and 5 mM was prepared and measured.

In the FT-IT spectra the ratio of the free- and H-bonded NH peaks were studied in the area between 3300 and 3500 cm^{-1}. In the^{1}H NMR spectra, the shift of the Ar-NH was monitored as a function of the dilution.

Infrared spectrum of the N-H stretches of 5 mM solutions of free ligand **D** (in red) and the complex [Rh(**D**)$_2$(NBD)](BF$_4$) (in blue). The free NH signal in the free ligand is observed as a rather sharp peak at 3430 cm^{-1}, while the H-bonded NH signal in the complex (and to a minor extend in the free ligand) is observed as a broad signal at 3360 cm^{-1}.[1]



Plot of the shift of the Ar-NH signal of free ligand **D** (in red) and complex [Rh(**D**)$_2$(NBD)](BF$_4$) (in blue) as function of the concentration (between 40 mM to 5 mM). In this concentration range the Ar NH-signal of the free ligand shifts due to self-aggregation via intermolecular hydrogen bonding at higher concentration. The Ar NH-signal of the coordinated ligand does not shift due to the intramolecular nature of the hydrogen bond.



General procedure for the hydrogenation experiments

In a typical hydrogenation experiment, a 15 ml pressure reactor containing a glass insert was subsequently charged, under inert conditions, with 0.5 ml of a 6 mM solution of the ligand in dichloromethane solution, 0.5 ml of a 2.5 mM solution of [Rh(NBD)$_2$](BF$_4$) in dichloromethane and 1 ml of a 0.125 M solution of the substrate in dichloromethane. The resulting mixture was exposed to a 10 bar H_2 atmosphere at room temperature for 18 h. Samples were drawn afterwards, and analysed by means of chiral GC. The columns used were; CycloSil-B (separation of the dimethylitaconate products) and CP-chiralsil-DexCB (separation of the products of N-(3, 4-dihydro-2-naphtalenyl)-acetamid and methyl 2-acetamidoacrylate).

[1] Y. Mido, *Spectrochim. Acta* **1973**, *29A*, 431.