Phosphabarrelene-modified Rh-catalysts: A new and selective route towards hydroxy-functionalized bicyclic imidazoles *via* tandem reactions

Patrick S. Bäuerlein,^{*a*} Ismael Arenas Gonzalez,^{*a*} Jarno J.M. Weemers,^{*a*} Martin Lutz,^{*b*} Anthony L. Spek,^{*b*} Dieter Vogt,^{*a*} and Christian Müller^{*a*}*

^a Schuit Institute of Catalysis, Laboratory for Homogeneous Catalysis, Eindhoven University of Technology, 5600 MB Eindhoven, The Netherlands. Fax: +31 40-2455054; Tel: +31-40-2474679; E-mail: c.mueller@tue.nl
 ^b Bijvoet Center for Biomolecular Research, Crystal and Structural Chemistry, Utrecht University, 3584 CH Utrecht, The Netherlands

Supplementary Material

General Remarks:

All chemicals were purchased from Aldrich, Acros or Merck and used as received. The liquids bought were degassed and the catalytical experiments were carried out under an atmosphere of dry argon or nitrogen using standard Schlenk techniques. NMR spectra were recorded on a Varian Unity Inova 500 (VT NMR) and Mercury 400-spectrometer. ¹H-NMR and ¹³C-NMR were referenced using residual solvent peaks. GC-MS analysis was formed on a Pegasus MS HP.

<u>GC-Analysis:</u> GC: Shimadzu GC 17a Column: Ultra 2 (crosslinked 5% Ph Me Siloxane), 25 m, inner diameter 0.20 mm Carrier gas: Helium 102 kPa or Column: Shimadzu GC-2010 Column: DB1, 30 m, inner diameter 0.32 mm Carrier gas: Helium 58.2 kPa

HPLC-Analysis: Pump: Shimadzu LC-20AD Eluents: n-hexane / 2- propanol mixture (95:5 v/v) Column: Chiralcel OD-H UV-VIS Detector: Shimadzu SPD-20A Wavelength: 200 nm Temperature: 25°C

1-(2-methylallyl)-1H-imidazole (3):

KOH (16.3 g, 290 mmol) was added to dimethyl sulfoxide (120 mL). The mixture was stirred for 5 min and 4.93 g (72.50 mmol) imidazole was subsequently added and stirred for another 45 min. After cooling (ice-bath) 3-chloro-2-methylpropene (4.7 mL, 48.30 mmol) was added dropwise. After 5 hours of stirring, water (120 mL) was poured into the reaction mixture. The aqueous layer was extracted with Et_2O (3 times 50 mL). The organic layers were combined, dried with Na_2SO_4 and concentrated.

¹H NMR (CDCl₃) δ (ppm): 7.44 (s, 1H), 7.05 (s, 1H), 6.86 (s, 1H), 4.94 (s, 1H), 4.78 (s, 1H), 4.42 (s, 2H). 1.68 (s, 3H).
¹³C NMR: 140.56, 137.49, 129.47, 119.21, 113.87, 53.04, 19.62.

MS:(m/z) 121.08 $[M]^+$. Yield: 60% (4.41 g).

Rh-catalyzed hydroformylation reactions:

Reactions in a 75-mL home-made stainless steel autoclave:

In a typical experiment, the autoclave was charged with a solution of 2.1 mg (8 μ mol) [Rh(acac)(CO)₂] and 20 eq. ligand in 5 mL of toluene. A dropping funnel connected to the reaction chamber of the autoclave was charged with a solution of 12 mmol (1.47 g) substrate in toluene (total volume 3 mL). The autoclave was pressurised with 20 bar CO/H₂ (1:2) and heated to preformation temperature and stirred for 2 h. Subsequently, the substrate was added to the catalyst solution and the reaction was started by elevating the temperature. After completion the reactor was cooled and the autoclave content was analysed by means of GC, chiral GC and HPLC. After removal of all volatiles and recrystallization from toluene **5** was obtained as an off-white solid (1.46 g, 9.6 mmol, 80%).

Reactions in the Amtec SPR 16:

Catalysis experiments under constant pressure were performed in the parallel autoclave system AMTEC SPR16, equipped with pressure sensors and a mass-flow controller and suitable for monitoring and recording gas uptakes throughout the reactions. The stainless steel autoclaves (12 mL) of the AMTEC SPR16 were flushed automatically with argon 6 times to remove oxygen traces (3 times at $T = 90^{\circ}C$, 3 times at room temperature). In the meanwhile, 2.1 mg of Rh(acac)(CO)₂ (8.0 µmol) and 20 equivalents of the monodentate ligands (L1-L4) were weighted and put in a Schlenk tube. Both were dissolved in 5 mL of dried and degassed toluene. The reactors were charged with a solution of this precatalyst (5 mL) under argon. The atmosphere was further exchanged with a 1:1 mixture of CO/H₂ (gas exchange cycle 1) and the reactors were heated to the desired preformation temperature and pressurized with CO/H₂ to the desired preformation pressure. The preformation of the catalyst under the applied conditions was performed for 2 hour. Subsequently, the substrate solution dissolved in toluene (total volume 3 mL) was injected and the desired temperature as well as the final pressure was adjusted and kept constant throughout the experiment. The gas uptake of CO/H₂ was monitored and recorded automatically (Figure S1). At the end of the catalysis experiments, the reactors were cooled to room temperature and the autoclave contents were analysed by means of GC, chiral GC and HPLC.



Fig. S1: Rh-catalyzed hydroformylation of **3** in toluene with ligands L1-L4. S:Rh = 1500:1, Rh:L = 1:20, $c_{Rh} = 1 \text{ mM}$, V = 8 mL, T = 80°C, p = 20 bar (CO/H₂ = 1:1).





Fig. S2: HPLC chromatogram of 5. Ratio: 1:2:2:1.

Separation of stereoisomers:

Fractions 1-4 were independently collected and analyzed by making use of the rather large differences in retention times. **5** (36 mg) was disolved in a mixture of n-hexane / 2- propanol mixture (95:5 v/v, 2 mL) and subject to HPLC analysis (100 μ l injections). The stereoisomers were collected in a glass tube under an argon atmosphere and the solvent was subsequently evaporated. This procedure was performed six times and the obtained residues were subject to further HPLC (Figure S3) and NMR spectroscopic (Figure S4 + S5) analyses.



Fig. S3: HPLC chromatograms of separated fractions 1-4.

Products:

4-(1H-imidazol-1-yl)-3-methylbutanal (4):



¹**H NMR** (CDCl₃) *δ* (ppm): 9.61 (s, 1H), 7.39 (s, 1H), 6.97 (s, 1H), 6.82 (s, 1H), 3.80 (m, 2H), 2.45 (m, 1H), 2.31 (m, 2H), 0.91 (s, 3H). ¹³**C NMR:** 200.41, 137.43, 129.59, 119.18, 52.09, 47.52, 29.76, 17.62. **MS:**(m/z) 151.09 [M]⁺

syn-8-hydroxy-6-methyl-5,6,7,8-tetrahydroimidazo[1,2-*a*]pyridine (*syn*-5)



¹**H** NMR (CDCl₃) δ (ppm): 7.04 (d, 1H, ${}^{3}J_{\text{H-H}} = 1.15$ Hz), 6.76 (d, 1H, ${}^{3}J_{\text{H-H}} = 1.1$ Hz), 4.89 – 4.85 (m, 1H, ${}^{3}J_{\text{H-H}} = 10.0$ Hz, ${}^{3}J_{\text{H-H}} = 6.6$ Hz), 3.98 – 3.94 (ddd, ${}^{3}J_{\text{H-H}} = 11.98$ Hz, ${}^{3}J_{\text{H-H}} = 5.11$ Hz, ${}^{3}J_{\text{H-H}} = 1.34$ Hz), 3.53 (t, 1H, ${}^{3}J_{\text{H-H}} = 11.56$ Hz), 2.36 – 2.31 (m, 1H), 2.24 – 2.12 (m, 1H), 1.66 – 1.57 (dt, 1H, ${}^{3}J_{\text{H-H}} = 12.62$ Hz, ${}^{3}J_{\text{H-H}} = 10.58$ Hz), 1.15 – 1.14 (d, 3H, ${}^{3}J_{\text{H-H}} = 6.67$ Hz). ¹³C NMR: 146.86, 128.07, 118.04, 61.04, 51.61, 37.94, 24.36, 18.44. Analysis calculated for C₈H₁₂N₂O: %C 63.13, %H 7.95, %N 18.41, found: %C 62.99, %H 7.82, %N 18.44. MS:(m/z) 151.09 [M]⁺



Fig. S4: ¹H NMR spectrum (CDCl₃, 400 MHz) of syn-5

anti-8-hydroxy-6-methyl-5,6,7,8-tetrahydroimidazo[1,2-a]pyridine (anti-5)



¹**H NMR** (CDCl₃) δ (ppm): 6.99 (s, 1H), 6.76 (s, 1H), 5.05 (t, H, ${}^{3}J_{\text{H-H}} = 3.3$), 4.07 – 4.03 (ddd, 1H, ${}^{3}J_{\text{H-H}} = 12.2$ Hz, ${}^{3}J_{\text{H-H}} = 5.07$ Hz, ${}^{3}J_{\text{H-H}} = 0.79$ Hz), 3.46 – 3.40 (t, 1H, ${}^{3}J_{\text{H-H}} = 11.67$ Hz), 2.72 – 2.59 (m, 1H), 2.20 – 2.16 (m, 1H), 1.77 – 1.69 (ddd, 1H, ${}^{3}J_{\text{H-H}} = 13.87$ Hz, ${}^{3}J_{\text{H-H}} = 12.30$ Hz, ${}^{3}J_{\text{H-H}} = 4.08$ Hz), 1.13 – 1.11 (d, 3H, ${}^{3}J_{\text{H-H}} = 6.71$ Hz). ¹³**C NMR:** 146.86, 128.07, 118.04, 61.04, 51.61, 37.94, 24.36, 18.44. Analysis calculated for C₈H₁₂N₂O: %C 63.13, %H 7.95, %N 18.41, found: %C 62.99, %H 7.82, %N 18.44. **MS:**(m/z) 151.09 [M]⁺



Fig. S5: ¹H NMR spectrum (CDCl₃, 400 MHz) of anti-5

X-ray crystal structure analysis of 5:

 $C_8H_{12}N_2O$, Fw = 152.20, colourless block, 0.33 x 0.18 x 0.12 mm³, monoclinic, C2/c (no. 15), $a = 13.4857(5), b = 8.0251(6), c = 19.0553(8) \text{ Å}, \beta = 129.266(2)^{\circ}, V = 1596.62(16) \text{ Å}^3, Z = 8, \beta = 129.266(2)^{\circ}, \lambda = 1596.62(16) \text{ Å}^3, \lambda = 129.266(2)^{\circ}, \lambda = 129.26(2)^{\circ}, \lambda = 129.26(2)^{\circ}, \lambda = 129.26(2)^{\circ}, \lambda = 129.26(2)^{\circ}, \lambda = 129.$ $D_x = 1.266 \text{ g/cm}^3$, $\mu = 0.09 \text{ mm}^{-1}$. 10235 Reflections were measured on a Nonius Kappa CCD diffractometer with rotating anode (graphite monochromator, $\lambda = 0.71073$ Å) up to a resolution of $(\sin \theta/\lambda)_{max} = 0.61 \text{ Å}^{-1}$ at a temperature of 150(2) K. Intensity integration was performed with EvalCCD^[1]. The SADABS^[2] program was used for absorption correction and scaling based on multiple measured reflections (0.88-0.99 transmission range). 1487 Reflections were unique ($R_{int} = 0.045$), of which 1122 were observed [I>2 σ (I)]. The structure was solved with Direct Methods using the program SHELXS-97^[3]. The structure was refined with SHELXL- $97^{[3]}$ against F² of all reflections. Non hydrogen atoms were refined with anisotropic displacement parameters. All hydrogen atoms were introduced in calculated positions and refined with a riding model. The structure was refined as a mixture of two stereoisomers on the same crystallographic site (see Fig. S6 and S7) with occupancies of 0.756(4):0.244(4). 139 Parameters were refined with 103 restraints (distance and angle restraints concerning the disorder and restraints to approximate isotropic behavior of the displacement parameters). R1/wR2 [I > $2\sigma(I)$]: 0.0584 / 0.1379. R1/wR2 [all refl.]: 0.0812 / 0.1481. S = 1.158. Residual electron density between -0.23 and 0.24 $e/Å^3$. Geometry calculations and checking for higher symmetry was performed with the PLATON program^[4].





Fig. S6: Molecular plots of the two stereoisomers present in the crystal structure of **5**, viewed along the crystallographic *b*-axis. The atoms O1A, C7A, C8A, and C10A have an occupancy of 0.756(4); the atoms O1B, C7B, C8B, and C10B have an occupancy of 0.244(4).



Fig. S7: Packing of 5 in the crystal, viewed along the crystallographic *a*-axis.

References:

- Duisenberg, A.J.M., Kroon-Batenburg, L.M.J., Schreurs, A.M.M. (2003). J. Appl. Cryst. 36, 220-229.
- [2] Sheldrick, G. M. (1999). SADABS: Area-Detector Absorption Correction, v2.10, Universität Göttingen, Germany.
- [3] G. M. Sheldrick, Acta Cryst. 2008, A64, 112-122.
- [4] A. L. Spek, J. Appl. Cryst. 2003, 36, 7–13.