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Cite this: DOI: 10.1039/c0xx00000x

www.rsc.org/xxxxxx

ARTICLE TYPE

Controlling Selectivity in the Consecutive Reaction Network of Aldoxime Hydrogenation to Primary Amines

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Received (in XXX, XXX) Xth XXXXXXXXX 20XX, Accepted Xth XXXXXXXXX 20XX

DOI: 10.1039/b000000x

Supplementary data

All chemicals were obtained from commercial suppliers and used as received. Substrates and reference compounds were obtained as follows: 2-ethylbutyraldehyde (Aldrich, 110094-250 ml, 92+ %), cyclohexanecarboxaldehyde (Aldrich, 10846-4, 98 %), (aminomethyl)cyclohexane (Fluka, 08454, > 97 %), nonylaldehyde (Acros, 357571000, 95 %), pivalaldehyde (ABCR, AB 133702, 97 %), cyclohexaneoxime (Merck Schuchardt, 8.22005.0100, > 98 %), 5-nonanone (Aldrich, 13 694-8, 98 %). The other aldoximes and ketoximes were prepared from the corresponding aldehydes and ketones as described below. Raney-Co was received as aqueous suspension. A sample was washed with de-ionized water under a nitrogen atmosphere until the pH-value of the effluent was neutral and dried for 30 h at 50 °C in a partial vacuum ($p < 1$ kPa). Due to its sensitivity to oxygen, Raney-Co was stored and handled under inert atmosphere throughout all further steps. The other catalysts (Ni/SiO_2, Ni/Al_2O_3, Pd/C, and Rh/C) were obtained as a powder and used as received (Table S1).

Table S1 Catalysts used explored for the hydrogenation of oximes

Catalyst [a]	Commercial name	Supplier	Product number
Ni/SiO_2	Pricat 2	Johnson Matthey	0470/2008
Ni/Al_2O_3	Pricat 3	Johnson Matthey	0470/2008
Raney-Co	Raney-Co 2724	Grace Davison	2724
Pd/C	Pd/C	Sigma-Aldrich	205699
Rh/C	Rh[C]	Johnson Matthey	117500

Due to the small particle size of the catalysts used for the slurry phase experiments (125-250 mm for Ni/SiO_2, Ni/Al_2O_3 and Rh/C, <90 mm for Pd/C), internal pore diffusion limitations were unlikely.[1-6]

3.1 Methods

^{1}H NMR spectra were recorded at 300 MHz on a Bruker DPX300 and at 400 MHz on a Bruker AV400. All spectra were recorded at room temperature. Chemical shifts are reported in parts per million [ppm], relative to the solvent residual peak: δ = 7.26 for [D1]-chloroform ($CDCl_3$).[7] The characterization of the signals is given as follows: s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Coupling constants are reported in Hertz [Hz]. In the case of mixtures of isomers, signals printed in parentheses refer to the minor product. – ^{13}C NMR spectra were recorded at 75 MHz on a Bruker DPX300 and 100 MHz on a Bruker AV400. All spectra were recorded at room temperature. Chemical shifts are reported in parts per million [ppm] relative to the central resonance of the solvent residual peak: δ = 77.16 for [D1]-chloroform ($CDCl_3$).[7] – EI-MS was performed on an SSQ7000. Signal intensities are reported in percent relative to the base peak (100 %). – HRMS was performed on an LTQ Orbitrap XL system. – EA (elemental analysis) was performed on a Vario EL. Calculated (calcd.) and found values for carbon (C), hydrogen (H) and nitrogen (N) are reported in wt%.

The metal content was determined by inductively coupled plasma atomic emission spectrometry (ICP-AES) using a Spectro Ciros Vision, ICP-OES after dissolution of the samples. – The surface area and the total pore volume of the catalysts were determined by nitrogen adsorption according to the Brunauer-Emmett-Teller method (BET) on a Sorptomatic 1900 (Carlo Erba Instruments). The samples were degassed under vacuum, while the temperature was increased at a rate of 5 °C/min. The samples were heated either for 8 hours to 250 °C (Ni/SiO_2, Ni/Al_2O_3, Ru/C, Pd/C, and Rh/C) or for 1 hour to 315 °C (Raney-Co). The nitrogen adsorption isotherms were measured subsequently at 77 K. – Adsorption experiments were conducted on a Sorptomatic 1900 (Carlo Erba Instruments) apparatus. Catalyst samples (about 2 g) were each placed in a gas cell capable of being evacuated. Prior to the sorption measurements, the samples were treated for 1 hour at 315 °C in a stream of hydrogen. Then, the gas cells containing the respective catalyst samples were evacuated for one hour at the same temperature. The samples were cooled subsequently to room temperature and equilibrated for one hour under argon. Subsequently, hydrogen was dosed into the gas cell. The amount of irreversibly adsorbed hydrogen was determined by the difference between the total and the reversible uptake.

3.2 Synthesis of aldoximes

Aldoximes were synthesized from the corresponding aldehydes by a modified literature procedure using aqueous hydroxylamine solution instead of hydroxylamine hydrochloride.[8]

General procedure: The aldehyde (0.50 mol) was added dropwise under vigorous stirring to a solution of 4.6 ml (4.96 g, 0.75 mol) 50 % aqueous hydroxylamine solution in 50 ml water.

The mixture was stirred over night at room temperature. The mixture was then extracted twice with 20 ml dichloromethane. The collected organic phases were dried over sodium sulphate and the solvent removed by evaporation to give the corresponding aldoxime.

Cyclohexanecarboxaldoxime:[9] 4.70 g (37.0 mmol, 74 %) of a solidifying colourless oil, obtained as a mixture of *E*/*Z*-isomers. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.24 (m, 5 H), 1.71 (m, 5 H), 2.19 (2.95) (ttd, 1 H, *J* = 14.8, 7.4, 3.7 Hz), 6.52 (7.31) (d, 1 H, *J* = 7.3 Hz) ppm. – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 24.7, 24.8, 25.3, 25.3, 28.9, 29.8, 33.0, 37.8, 154.2, 154.9 ppm. – EI-MS: *m*/*z* (%) = 127 (10) [M^+], 110(26), 95 (23), 85 (55), 83 (100), 72 (22), 67 (55), 59 (86).

2-Ethylbutyraldoxime:[9] 5.05 g (43.8 mmol, 88 %) of a colourless liquid, obtained as a mixture of *E*/*Z*-isomers. – ^{1}H NMR (300 MHz, $CDCl_3$) δ = 0.90 (dt, 6 H, *J* = 2.7, 7.4 Hz), 1.44 (m, 4 H), 2.09 (2.96) (m, 1 H), 6.48 (7.22) (d, 1 H, *J* = 8.2 Hz) ppm. – ^{13}C NMR (75 MHz, $CDCl_3$) δ = 11.6, 25.3, 38.1, 43.0, 155.6, 156.3 ppm. – $C_6H_{13}NO$; calcd.: C 62.57, H 11.38, N 12.16; found: C 62.08, H 11.44, N 12.31.

Nonanaldoxime:[10] 7.55 g (48.0 mmol, 96 %) of a colourless solid, obtained as a mixture of isomers. – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.88 (t, 3 H, *J* = 6.5 Hz), 1.27 (m, 10 H), 1.49 (tt, 2 H, *J* = 6.9 Hz), 2.19 (2.38) (dt, 2 H, *J* = 5.6, 7.4 Hz), 7.42 (6.73) (t, 2 H, *J* = 6.1 Hz) ppm. – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.1, 22.7, 25.0, 26.0, 26.5, 29.1, 29.2, 29.2, 29.3, 29.4, 29.5, 31.8, 152.4, 153.0 ppm. – EI-MS: *m*/*z* (%) = 157 (5) [M^+], 141 (10), 127 (8), 110 (7), 100 (18), 96 (14), 86 (21), 83 (32), 72 (28), 69 (37), 59 (100), 57 (54), 55 (53). – $C_9H_{19}NO$; calcd.: C 68.74, H 12.18, N 8.91; found: C 68.74, H 12.28, N 8.76.

Pivalaldoxime: 4.97 g (49.1 mmol) of a colourless solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.10 (s, 9 H), 7.35 (s, 1 H), 8.38 (s, 1 H) ppm. – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 27.4, 33.7, 159.1 ppm – HRMS: calcd.: 102.09134 ($C_5H_{12}NO$; M^+ + H); found: 102,09121.

3.3 Synthesis of ketoximes

5-Nonanketoxime:[11] To a round bottom flask containing a solution of 15.4 g (0.233 mol) of a 50 % aqueous hydroxylamine solution in 25 ml water was added 15.1 g (0.106 mol) nonanone and the resulting mixture stirred at room temperature for 24 h. The mixture was then extracted three times with 15 ml dichloromethane. The collected organic phases were dried over sodium sulphate and the solvent removed by evaporation to give 16.2 g (0.103 mol, 97 %) of colourless oil. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.89 (t, 3 H, *J* = 7.1 Hz), 0.90 (t, 3 H, *J* = 7.0 Hz), 1.32 (m, 4 H), 1.47 (m, 4 H), 2.16 (t, 2 H, *J* = 7.1 Hz), 2.32 (m, 2 H, *J* = 7.8 Hz), 9.79 (bs, 1 H) ppm. – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 13.7, 13.7, 22.4, 22.9, 27.2, 27.7, 28.4, 33.7, 161.6 ppm.

3.4 Synthesis of nitriles

General procedure: Aldoxime and acetic anhydride were placed in a round bottom flask, equipped with a magnetic stirrer and reflux condenser. The mixture was stirred for 8 hours at 100° C. The reaction mixture was cooled to room temperature and poured into solution of sodium hydrogen carbonate under vigorous stirring. Then, diethyl ether was added to the mixture. The organic layer was separated and dried over magnesium sulphate. The solvent was removed under vacuum and the product purified by distillation.

Cyclohexyl cyanide:[12] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.42 (m, 4 H), 1.66 (m, 4 H) 1.82 (m, 2 H), 2.59 (m, 1 H) ppm. – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.1, 25.3, 28.0, 29.5, 122.6 ppm.

2-Ethylbutyl cyanide:[13] ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.05 (t, 6 H, *J* = 7.4 Hz), 1.60 (dq, 4 H, *J* = 7.3 Hz), 2.39 (tt, 1 H, *J* = 7.1 Hz) ppm. – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.6, 25.2, 35.0, 122.2 ppm.

3.5 Synthesis of Schiff bases

1-Cyclohexyl-N-(cyclohexylmethylene)methanamine: To a solution of 40.4 g (0.36 mol) cyclohexanecarboxaldehyde in 100 ml chloroform was added dropwise 40.8 g (0.36 mol) cyclohexanemethylamine under vigorous stirring. The mixture was stirred over night at room temperature, dried over magnesium sulphate and filtrated. The solvent was then removed under partial vacuum and the product obtained as colourless liquid. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.85 (m, 2 H), 1.19 (m, 8 H), 1.64 (m, 11 H), 2.11 (m, 1 H), 3.13 (d, 2 H, *J* = 6.4 Hz), 7.37 (d, 1 H, *J* = 5.2 Hz) ppm. – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 25.4, 25.9, 26.0, 26.6, 29.8, 31.2, 38.4, 43.4, 68.3, 168.9 ppm. – HRMS: calcd.: 208.20598 ($C_{14}H_{26}N$, M^+ + H); found: 208,20551.

2-Ethyl-N-(2-ethylbutylidene)butan-1-amine: A solution of 506.0 mg (5.0 mmol) 2-ethylbutylamine in 2 ml dichloromethane was added dropwise under stirring to a suspension of magnesium sulphate in 10 ml dichloromethane. The apparatus was equipped with a drying tube charged with calcium chloride and the mixture heated to reflux for 5 min. The mixture was allowed to rest for 14 h and then heated to reflux for another 1 h. After filtration, the solvent was evaporated carefully under reduced pressure to give 810.7 mg (4.43 mmol, 85 %) of a colourless oil. – ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.83 (t, 6 H, *J* = 6.8 Hz), 0.85 (t, 6 H, *J* = 7.2 Hz), 1.27 (m, 4 H), 1.41 (m, 4 H), 1.51 (m, 1 H), 2.01 (m, 1 H), 3.25 (d, 2 H, *J* = 6.4 Hz), 7.32 (d, 1 H, *J* = 6.8 Hz) ppm. – ^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.8, 11.5, 23.8, 25.1, 41.6, 48.2, 64.4, 168.9 ppm. – HRMS: calcd.: 184,20598 ($C_{12}H_{26}N$, M^+ + H); found: 184,20517.

3.6 Catalyst characterization

Prior to the performance tests in catalysis, the catalysts were fully characterized (Table 3). The BET surface area of Ni/SiO_2 and Ni/Al_2O_3 was high (106.9 m^2/g and 114.3 m^2/g, respectively), but the number of exposed metal atoms was very small (0.6 % and 0.2 % dispersion, respectively). Electron microscopy showed that the metal particles were encapsulated in the oxide matrix, which may be the origin of the initiation period in hydrogenation (*vide infra*). The Raney catalysts had a lower BET surface area of 54.2 m^2/g and 61.4 m^2/g (Raney-Ni and Raney-Co, respectively), whereby a relative large fraction of the surface was composed of metal atoms (23.3 m^2/g and 4.6 m^2/g, respectively). Note the relatively low content of active phase, which was 62.4 wt% and 51.2 wt% metal, respectively. For the noble metal catalysts, the carbon supports provided a high surface area. The metal nanoparticles were highly dispersed for Pd/C and Rh/C (40.6 %

and 46.7 %, respectively), while Ru-Re/C had a much lower dispersion (6.8 %).

Table S2 Characterization of the catalysts used in this study

Catalyst	Metal content [wt%]	BET surface area [m^2/g]	Specific pore volume [cm^3/g]	M_s [a] [mol/g]	Metal surface area [m^2/g]	Dis-per-sion [%]	Diameter metal particles [b] [nm]
Ni/SiO_2	46.6 Ni 9.9 Cr	106.9	0.17	48.6	1.9	0.6	3.2 – 18.8 (6.8)
Ni/Al_2O_3	19.5 Ni	114.3	0.40	5.4	0.2	0.2	2.4 – 10 (5.5)
Raney-Co	51.2 Co	61.4	0.15	234.6	4.6	1.4	-
Pd/C	6.1 Pd	682.6	0.65	232.8	11.0	40.6	3.1 – 5.0 (4.8)
Rh/C	0.41 Rh	844.0	0.45	36.3	0.8	46.7	2.0 – 18 (2.4)

[a] Number of surface metal atoms

[b] Range of particle diameters and maximum in the particle size distribution of the metal crystallites, based on statistical evaluation of particle size in electron microscopy images.

3.7 Oxime hydrogenation

All data refer to the hydrogenation of 2-ethylbutyraldoxime at p_{H2} 40 bar and 140 °C, if not stated otherwise. The maximum rate of reaction estimated at 50 % conversion placed the catalysts into the following sequence of decreasing activity per mass unit catalyst: Raney-Ni > Raney-Co > Rh/C > Ni/SiO_2 > Ni/Al_2O_3 > Pd/C > Ru-Re/C (S2). The intrinsic activity per surface metal atom decreased in the sequence Ni/Al_2O_3 > Rh/C > Ni/SiO_2 > Raney-Co > Ru-Re/C > Pd/C > Raney-Ni.

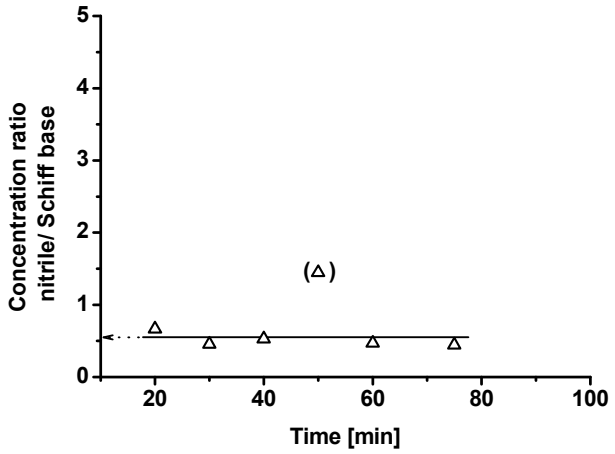

Fig. S1 Ratio of the concentrations of nitrile and Schiff base *vs*. the reaction time for the hydrogenation of 2-ethylbutyraldoxime (Ni/SiO_2, p_{H2} 40 bar, 140 °C).

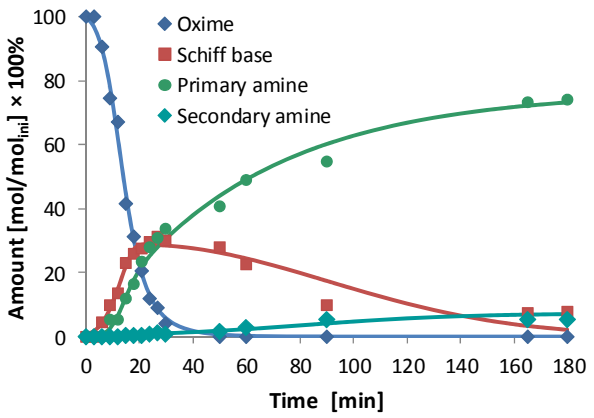

Fig. S2 Time-concentration diagram for the hydrogenation of 2-ethyl¬butyr¬aldoxime in the presence of water (Ni/SiO_2, p_{H2} 40 bar, 140 °C).

3.7 Catalyst pre-treatment

The start-up procedure was also changed. A mixture of 2-ethyl¬butyr¬aldoxime, Ni/SiO_2, and thf was pressurized with hydrogen at room temperature and then heated to reaction temperature. The reaction proceeded very similar to the reaction with our standard start-up procedure.† Full conversion of 2-ethyl¬butyr¬aldoxime was obtained after 60 min. The selectivity towards 2-ethylbutylamine increased to 84.5 %, while trace amounts of the intermediate Schiff base (2.1 %) remained unconverted. Hence, presence of hydrogen from the start of the reaction leads to an enhanced selectivity towards the primary amine, but slower conversion of Schiff base.

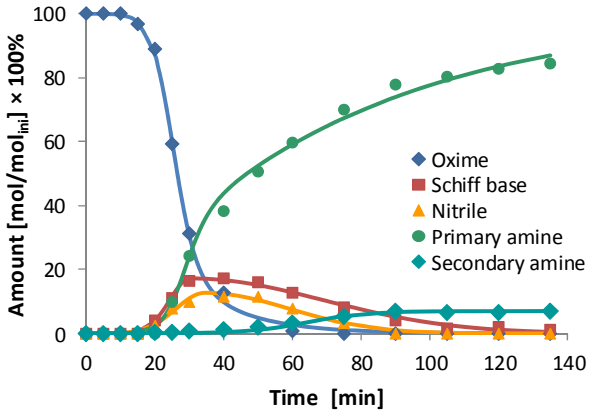

Fig. S3 Time-concentration diagram for the hydrogenation of 2-ethyl¬butyr¬aldoxime, whereby the reactor was pressurised with hydrogen at room temperature and then heated to 140°C (Ni/SiO_2, p_{H2} 40 bar).

3.8 Mechanistic model

A search of the Cambridge Crystallographic Database [14] showed that compounds with structures similar to those proposed in our mechanistic model have been isolated and crystallized. Schematic representations of selected examples are shown in Figure S8.

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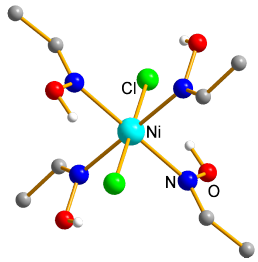
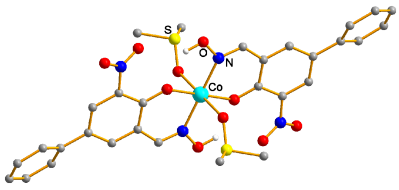
Table S2 Schematic representation of selected examples for stable model complexes and reference code in the Cambridge Crystallographic Database. [a]

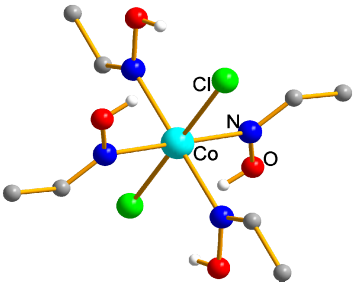
Oxime complexes (structure type **A**)



ACOXNU10

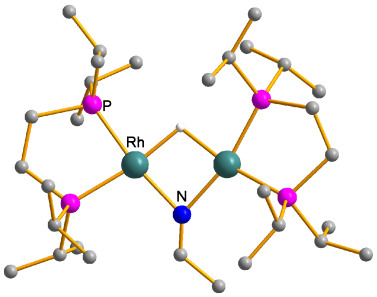


BACNOJ

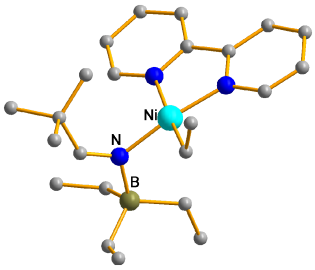


QEDKIT

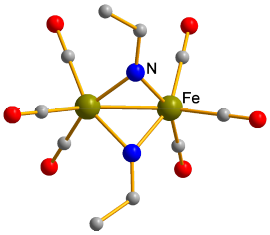
Alkylideneamido complexes (structure type **B**)



VUSYUD

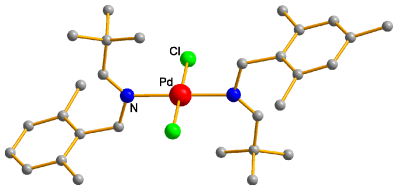


BENIIB

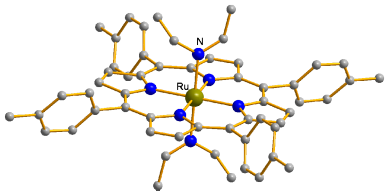


ETAMFE

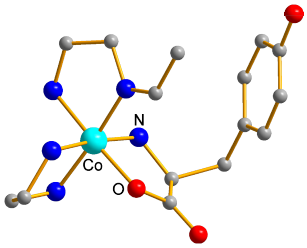
Schiff base complexes (structure type **F**)



LIQVUD

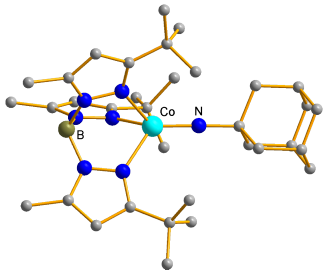


WOFZEW

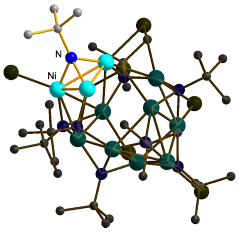


BOXRUB

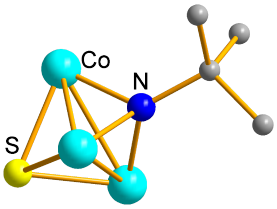
Alkylimino complexes (structure type **D**)



YALHOJ

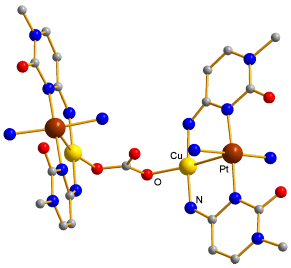


REPHEZ



GEWNOL[b]

(Alkylamido)alkylamino complexes (structure type **E**)



REBBIJ

[a] Complexes of row 3 transition metals (Co, Ni, Fe) and, for comparison, selected row 4 and 5 metals (Cr, Rh, Pt) were considered; [b] Cp ligands are omitted for the sake of clarity.

Acknowledgements

We acknowledge Yevgen Berezhanskyy and Alexandra Keldenich for synthesizing the oximes and Schiff bases, Timo Koch for introducing H.V. into the chemistry under high pressures. We would also like to thank Dr. Weirich and Dr. Reinhold, *Gemeinschaftszentrum für Elektronenmikroskopie* (GfE), RWTH Aachen University for the electron microscopy images.

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