Article

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ACS Catal., **Just Accepted Manuscript** • DOI: 10.1021/acscatal.5b01955 • Publication Date (Web): 12 Nov 2015

Efficient base-free hydrogenation of amides to alcohols and amines catalysed by well-defined pincer imidazolyl-ruthenium complexes

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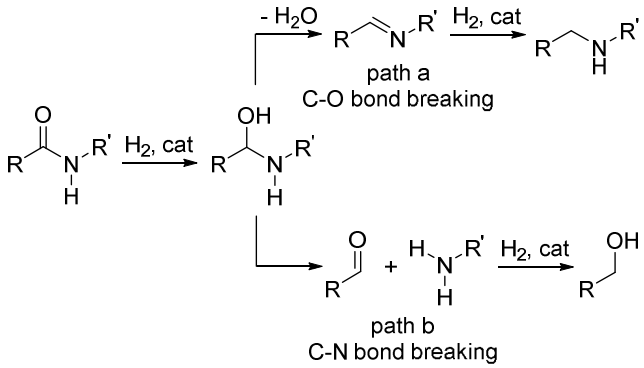
ABSTRACT: Novel homogeneous ruthenium catalysts bearing an imidazolylaminophosphino pincer ligand have been synthesized. The active catalyst allows for the hydrogenation of a range of amides under base-free conditions to afford the corresponding alcohols and amines in high yields.

KEYWORDS Amide hydrogenation, Ruthenium, bifunctional catalysis, pincer complexes, homogeneous catalysis.

INTRODUCTION

Amines constitute an important class of compounds, which play a key role in numerous chemical processes. Nowadays, they are commonly used on bulk scale as building blocks for dyes, drugs, agrochemicals, polymers and other materials. Among the methods amenable to the synthesis of amines,[1] catalytic reductions of nitroarenes, nitriles and reductive amination of carbonyl compounds prevail in industry. In addition, catalytic hydrogenation of amides using molecular hydrogen[2] offers an atom-economic and waste-free methodology (Scheme 1, path a) compared to the traditional reduction using metal hydrides[2a] or boranes[3] or silanes.[4]



Scheme 1. Possible Reaction Pathways for the Reduction of Amides with Hydrogen.

Unfortunately, due to the low electrophilicity of the carbonyl group, the reduction of amides with molecular hydrogen occurs in general at elevated pressures and very high temperature, although recent improvements using heterogeneous catalysts have been achieved.[5] However, a drawback associated with the use of this latter catalysts is their incompatibility with aromatic groups and multiple CC- and CX-bonds which are likewise reduced. In order to overcome these problems the development of more active molecular-defined catalysts is desirable. In this respect, the recent work on ruthenium complexes with 1,1,1-tris(diphenylphosphinomethyl)ethane (Triphos®) as ligand, which operate in the presence of an acid co-catalyst, is also noteworthy.[6] Yet it has a rather limited scope and still requires temperatures above 200 °C.

Recently, different homogeneous catalysts which rely on metal-ligand cooperation (bifunctional catalysis)[7] have been disclosed for the reduction of amides under much milder conditions. Here, alternative reactivity is observed and the initial reduction of the carboxylic group is followed by collapse of the intermediate hemiaminal to afford the corresponding alcohol and amine (Scheme 1, path b).[8] Notably, this transformation offers the possibility to access amines and alcohols from amides and might be used as a selective deprotection methodology. The structures of the known catalysts for amide hydrogenolysis are shown in Chart 1: with the exception of Milstein's and Bergen's BH_4-modified complexes, all catalysts require an excess of base to provide good activity.[9] In the past decade pincer ligands able to engage in bifunctional catalysis have experienced widespread applications in catalysis.[10] So far, different sets of soft and hard donors have been combined and the presence of hemilabile groups (NR_2, Py) has been shown to be advantageous in ester[11] and amide reduction.[9a]

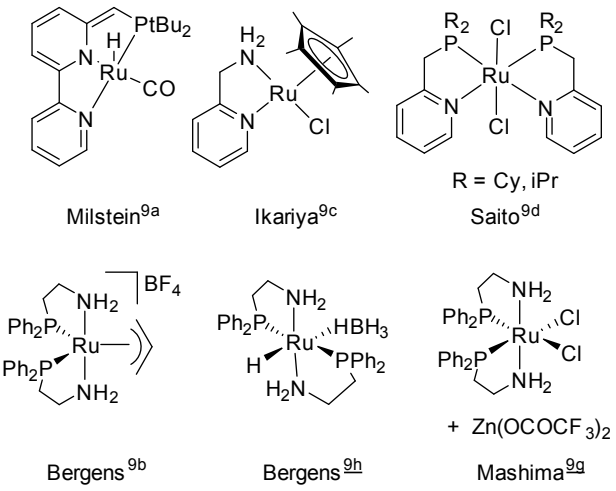


Chart 1. Bifunctional Ruthenium Catalysts which Promote the Hydrogenation of Amides according to Path b in Scheme 1.

Following our previous work concerning the synthesis of bidentate imidazolyl phosphines and their succesful application in the ruthenium-catalyzed hydrogenation of carboxylic acid derivatives,[12] we considered the synthesis of imidazole-based pincer ligands (P(NH)Im pincer motif). 1-Methylimidazol, with a pK_{aH} of 7.0, has a basicity which is intermediate between that of the side arm nitrogen donors so far employed in *N*NP pincer ligands such as a pyridine (pyridine pK_{aH} = 5.2) or an amine moietiy NR_2 (fully saturated aliphatic amines have pK_{aH} values mostly within the range 9 - 11).[13]

RESULTS AND DISCUSSION

The NNP pincer ligand, 3-(di-*tert*-butylphosphino)-*N*-((1-methyl-1H-imidazol-2-yl)methyl)-propylamine **1** (Scheme 2), is easily assembled in a one-pot two step synthesis starting from commercially available 1-methyl-2-imidazolecarboxaldehyde and 3-(di-*tert*-butylphosphine) propylamine.[14] For the preparation of the corresponding ruthenium complex, $[RuHCl(CO)(PPh_3)_3]$ was reacted with the ligand to afford [RuHCl(CO)(3-(di-*tert*-butylphosphino)-*N*-((1-methyl-1H imidazol-2-yl)methyl)propylamine)] **2** after displacement of PPh_3 in 89 % yield, as a mixture of two isomers in a 3:1 ratio: each complex is characterized by a singlet in the $^{31}P\{^1H\}$ NMR at 78.11 ppm (major) and 74.19 ppm (min), respectively. The signals of the hydride ligand in the ^1H NMR appear as doublets at -15.91 (J_{HP} = 25.2 Hz) (major) and -16.25 (J_{HP} = 23.0 Hz) (minor). The value of the J_{HP} indicates that the hydride ligand is located, in both isomers, *cis* to the phosphorus donor and their chemical shifts suggest that they must be *trans* to a donor of low *trans* influence.[15] Figure 1 illustrates the X-ray structure of the major isomer,[16] in which the ligand is coordinated to ruthenium in a meridional fashion with the CO ligand *trans* to the central aliphatic nitrogen. The metal hydride and the hydrogen on the nitrogen are located *syn* as to the plane defined by the pincer ligand and ruthenium. Because a NOESY cross signal is present between the two hydrogens for the major isomer in solution, which is instead absent for the minor, the solid structure is assigned to the major isomer *syn*-**2**. Due to the similarity of the spectroscopic features of the two isomers, the minor must be the one were the two hydrogen are oriented *anti* to each other, which is therefore denoted as *anti*-**2**.

Preliminary catalytic tests to assess whether the new complex **2** is active in amide hydrogenation were run on the benchmark substrate benzanilide **4**. The reaction proceeded smoothly affording benzyl alcohol **5** and aniline **6** in quantitative yields using 1 mol% of complex **2** in *iso*-propanol at 50 bar of H_2 and 150 °C in the presence of a slight excess of base (5 eq to Ru) (entry 1, Table 1).

Scheme 2. Synthesis of Pincer Ligand (1) and its Ruthenium Complexes (2) and (3).

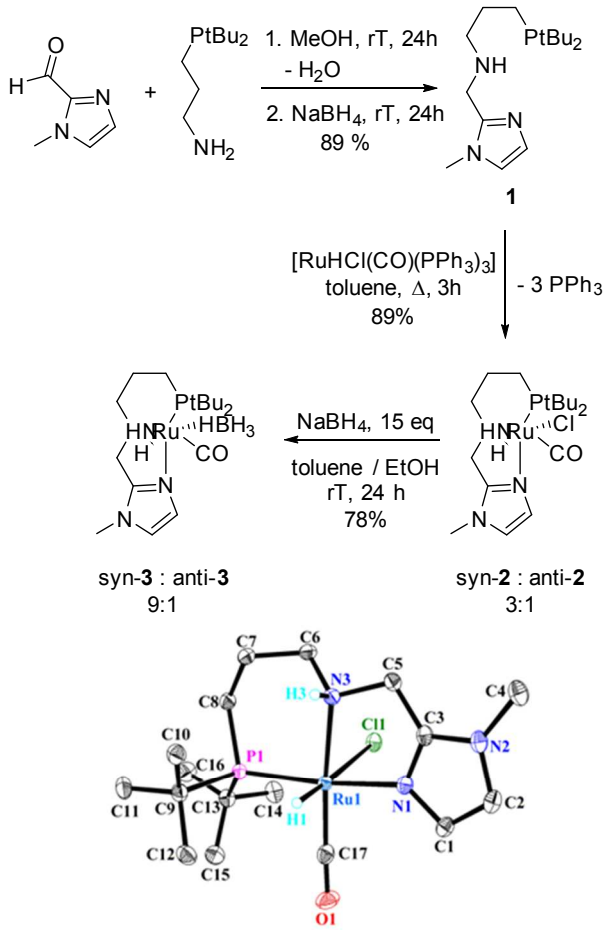
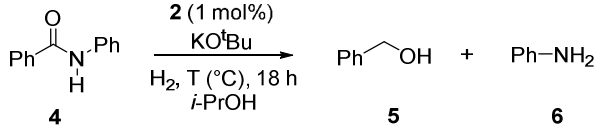


Figure 1. X-ray structure of ***syn*-2** with thermal ellipsoids drawn at the 30% probability level. Hydrogen atoms other than H1 and H3 are omitted for clarity. Selected bond lengths (Å): Ru(1)-N(1) 2.1137(15); Ru(1)-N(3) 2.2219(16); Ru(1)-P(1) 2.2995(6); Ru(1)-Cl(1) 2.5741; Ru(1)-H(1) 1.52(2); Ru(1)-C(17) 1.809(2); and angles (°): N(1)-Ru(1)-N(3) 77.15(6); N(3)-Ru(1)-P(1) 94.14(4).

Indeed, one equivalent of base was enough to secure quantitative yields of **5** and **6** (entry 2, Table 1), while no reaction took place in the absence of base (entry 3, Table 1). To our delight, the catalyst was equally effective under milder conditions (30 bar of H_2 and 120 °C), even when

the catalyst loading was reduced to 0.5 mol % (entries 4 and 5, Table 1). The reaction conditions could be mitigated further to 15 bar and 100 °C with only a minor erosion of yields (94%, entry 6, Table 1) but reducing the temperature to 80 °C led to detrimental results (9% yield, entry 7, Table 1).

Table 1. Hydrogenation of Benzanilide (4) with Ruthenium Complex (2): Optimization of Reaction Conditions



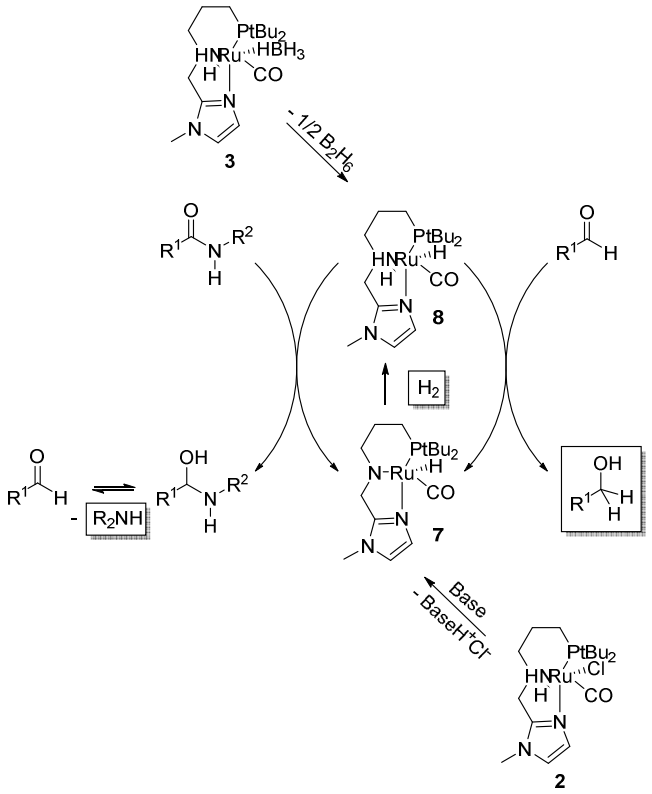
4 5 6

Entry[a]	H_2 (bar)[b]	T (°C)	KO^{t}Bu (mol%)	Conv. (%)[c]	**5** (%)[c]	**6** (%)[c]
1	50	150	5	100	>99	>99
2	50	150	1	100	>99	>99
3	50	150	-	-	-	-
4	30	120	1	100	>99	>99
5[d]	30	120	1	100	>99	>99
6	15	100	1	95	94	94
7	30	80	1	21	9	9

[a] Standard reaction conditions: benzanilide **4** (0.5 mmol, 100.62 mg), complex **2** (0.005 mmol, 1 mol%), KO^{t}Bu (1-5 mol%), dry Isopropanol (2 ml) under H_2. [b] Pressure of hydrogen at room temperature. [c] Conversion of **4** and yields of **5** and **6** were calculated by GC using hexadecane as external standard. [d] The reaction was carried out with 0.5 mol% of catalyst.

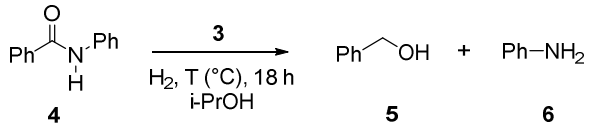
These preliminary experiments suggest that the active catalytic species **7**, once formed by dehydrochlorination of the catalyst precursor **2** (Scheme 3), might promote the reduction of amides even in the absence of base. Therefore, we prepared the catalyst **3** in which the Cl ligand had been replaced by BH_4^- (Scheme 2), thus circumventing the need to use base to generate the active catalyst (Scheme 3).[17] Complex **3** was easily prepared in 78% isolated yield by treating **2** with an excess of $NaBH_4$. It was obtained as a white solid which can be handled in air, although it is sensitive to oxygen in solution and is better kept under argon if stored for a prolonged time. The complex was obtained as a mixture of two isomers in a a 90:10 ratio with singlet signals at 82.44 ppm (major), and 79.59 ppm (minor) in the $^{31}P\{^1H\}$ NMR. The coordinated hydrides appear as doublets in the ^1H NMR, at -13.00 ppm (major, JHP = 22.7 Hz) and -13.56 ppm (minor, J_{HP} = 19.6 Hz), while the BH_4^- group gives rise to a broad four proton resonance at -1.83 ppm. The chemical shift and the peak shape are indicative of a η^1-coordination mode, with a rapid exchange (on the NMR time scale) of the bridging and terminal hydrides.[18] Based on the similarity of the spectroscopic features between **2** and **3**, it is reasonable to assume that the same arrangement of ligands in the ruthenium coordination sphere is present in **3** as in **2**, with the pincer ligand arranged in a meridional fashion and the hydride and BH_4- group disposed *trans* to each other in both isomers. Although the NOESY spectrum shows a through-space interaction between the hydride and the hydrogen on nitrogen in the major isomer for which the *syn* arrangement of the two might be then proposed, a cross peak in the same area could be observed for the hydride of the minor isomer, for which however the corresponding N*H* signal in the ^1H NMR could not be identified because of overlapping. Therefore we are unable to unequivocally assign the *syn* and *anti* configurations of **3**.

Scheme 3. Proposed Catalytic Cycle for Amide Reduction Promoted by Complexes (2) and (3)



Reduction of benzanilide **4** in *iso*-propanol with 0.5 mol % of **3** indeed afforded quantitative yields of benzyl alcohol **5** and aniline **6** under the conditions previously optimized for **2**, 120 °C, 30 bar H_2, 18 hours, with no added base (entry 6, Table 2). The performance of catalyst **3** turned out to be affected by hydrogen pressure and temperature in the same way as **2** (Table 2). A striking difference in catalyst performance was observed in *iso*-propanol compared to other solvents, where either no reaction took place (entries 4-6, Table 3) or a 20% conversion was obtained at best with toluene (entry 7, Table 3). To test for transfer hydrogenation, a control experiment was performed in the absence of hydrogen gas at 120 °C using 0.5 mol% of **3** (entry 14, Table 2). However, no reduction of benzanilide **4** was detected excluding the possibility that *iso*-propanol might act as hydrogen donor.

Table 2. Hydrogenation of Benzanilide 4 with Ruthenium Complex (3): Optimization of Reaction Conditions



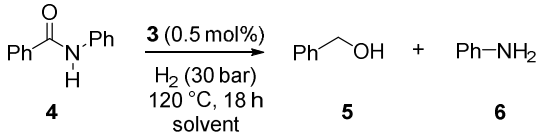
4 **5** **6**

Entry[a]	H_2 (bar)[b]	T (°C)	**3** (mol%)	Conv. (%)[c]	**5** (%)[c]	**6** (%)[c]
1	50	150	1	100	>99	>99
2	50	150	0.5	100	>99	>99
3	50	150	0.25	-	-	-
4	30	120	1	100	>99	>99
5[d]	30	120	1	100	99	99
6	**30**	**120**	**0.5**	**100**	**99**	**99**
7[d]	30	120	0.5	26	25	25
8	30	100	0.5	-	-	-
9	30	100	1	100	>99	>99
10	30	80	1	56	38	39
11	15	120	1	100	>99	>99
12	15	120	0.5	64	63	64
13	15	100	1	84	80	81
14[e]	-	120	0.5	-	-	-

[a] Standard reaction conditions: benzanilide **4** (0.5 mmol, 100.62 mg), complex **3** (0.005 mmol, 1 mol%), dry Isopropanol (2 ml) under H_2. [b] Pressure of hydrogen at room temperature. [c] Conversion of **4** and yields of **5** and **6** were calculated by GC using hexadecane as external standard. [d] The reaction time was 3 h. [e] The reaction was carried out in a pressure tube without hydrogen.

Next, several primary, secondary and tertiary amides were tested in the presence of catalyst **3**. All substrates were reduced affording excellent yields of the desired amine and/or alcohol under the optimised conditions (0.5 mol % of **3**, 30 bars of H_2, 120 °C, in *iso*-propanol over 18 hours; Table 4). For the less electrophilic amides, either a slightly higher catalyst loading, up to 2 mol % or more forcing conditions (50 bars of H_2 and 150 °C) or a combination of both, allowed to achieve very good yields. For example, reduction of benzyl- (entry 3, Table 4) and fluoro- and chloro-substituted amides (entries 7-10 and 15, Table 4) proceeded smoothly. Worth mentioning is the possibility to effectively reduce heterocyclic amides, like 3-acetamidopyridine (entry 11, Table 4), three derivatives of nicotinic acid (entries 18-20, Table 4) including the primary amide nicotinamide, and *N*-acetyl-1,2,3,4-tetrahydroquinoline, giving 1,2,3,4-tetrahydroquinoline in quantitative yield (entry 16, Table 4). In addition, aliphatic tertiary amides such as *N,N*-dimethyloctanamide could be hydrogenated as well in excellent yield (entry 17, Table 4).

Table 3. Hydrogenation of Benzanilide 4 with Ruthenium Complex (3): Influence of Solvent



4 **5** **6**

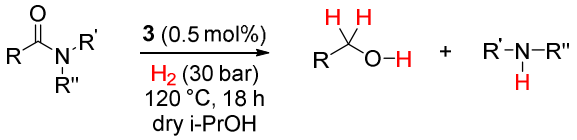
Entry[a]	Solvent	Conv. (%)[b]	**5** (%)[b]	**6** (%)[b]
1	*i*-PrOH	100	>99	>99
2	*i*-PrOH/H_2O (10:1)	3	2	2
3	EtOH	8	7	6
4	MeOH	-	-	-
5	THF	-	-	-
6	1,4-Dioxane	-	-	-
7	Toluene	20	19	19

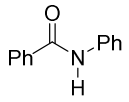
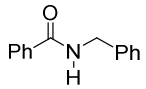
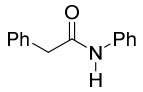
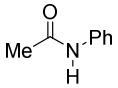
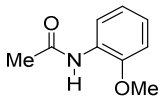
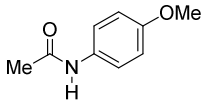
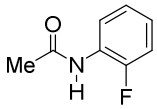
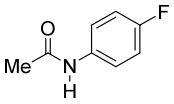
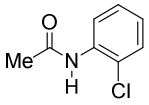
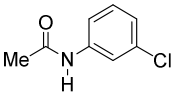
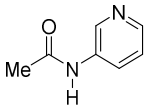
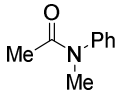
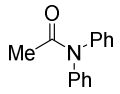
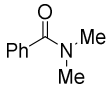
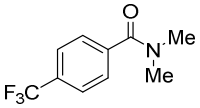
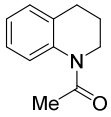
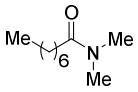
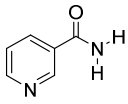
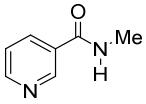
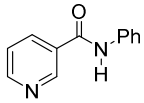
[a] Standard reaction conditions: benzanilide **4** (0.5 mmol, 100.62 mg), complex **3** (0.0025 mmol, 0.5 mol%), dry solvent (2 ml), H_2 (30 bar) at 120 ºC over 18 h. Pressure of hydrogen at room temperature. [b] Conversion of **4** and yields of **5** and **6** were calculated by GC using hexadecane as external standard.

To date, the hydrogenolysis of primary amides has been scarcely investigated[9] and no general catalyst exists for such transformations. Although **3** alone failed to catalyse the reduction of less reactive benzamide and octanamide, addition of 10 mol% of KO^{t}Bu at 150 °C under 50 bars of H_2 gave satisfactory yields of the desired products. The positive influence of base is in agreement with the recent work by Bergens et *al.*[9f,h] and can be ascribed to the increased nucleophicility of the coordinated hydride in the ruthenium dihydride which has been further deprotonated at the ligand aliphatic nitrogen. As shown in Table 5 various primary and secondary amides underwent successful hydrogenolysis.

More specifically, *N*-methyl and *N*-cyclohexylbenzamide were hydrogenated in very good yields (entries 1 and 2, Table 5). Primary amides such as benzamide, *p*-dimethylamino- and *p*-methoxybenzamide afforded moderate to good yields of the corresponding benzyl alcohols (entries 3-5, Table 5), which were clearly dependent on the electrophilicity of the carbonyl group. Although in moderate yield, the primary amide 2-furamide was reduced as well (entry 6, Table 5). Last but not least, octanamide, an aliphatic poor-reactive primary amide, could be reduced to octanol in good yield (61%, entry 7, Table 5).

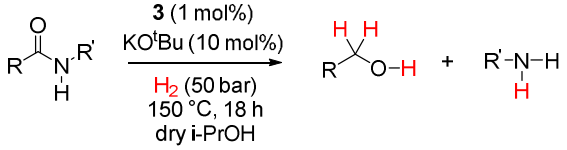
Table 4. Hydrogenation of Amides Catalyzed by Complex (3) Without Added Base.

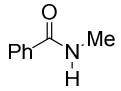
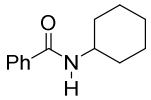
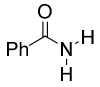
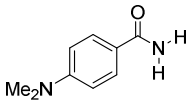
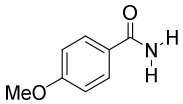
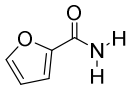
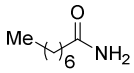


Run[a]	Amide	Conv. (%)[b]	Alcohol (%)[b]	Amine (%)[b]
1		100	>99	>99
2		75	70	67
3[c]		100	93	94
4		100	>99	>99
5		100	>99	>99
6		100	98	98
7[d]		100	>99	>99
8[e]		93	93	89
9[d]		100	98	97
10[f]		100	99	98
11		100	97	96
12		96	83	83
13		100	96	96
14		100	96	n.d.
15[e]		100	>99	n.d.
16		100	99	99
17		92	90	n.d.
18[c]		100	95	n.d.
19[g]		93	82	n.d.
20		100	99	99

[a] Reaction conditions: amide (0.5 mmol), complex (**3**) (0.0025 mmol, 0.5 mol%, 1.10 mg), dry *iso*propanol (2 mL), H2 (30 bar) at 120 °C over 18 h. Pressure of hydrogen at room temperature in all cases. [b] Conversion and yields were calculated by GC using hexadecane as external standard. [c] The reaction was carried out using 2 mol% of catalyst under 50 bar of H2 at 150 °C. [d] The reaction was carried out using 1 mol% of catalyst. [e] The reaction was carried out using 1 mol% of catalyst under 50 bar of H2 at 150 °C. [f] The reaction was carried out using 2 mol% of catalyst. [g] The reaction was carried out using 0.5 mol% of catalyst under 50 bar of H2 at 150 °C. (n.d. = not detected).

Table 5. Hydrogenation of Primary and Secondary Amides Catalyzed by Complex (3) in the Presence of Added Base.



Run[a]	Amide	Conv. (%)[b]	Alcohol (%)[b]	Amine (%)[b]
1		100	92	n.d.
2		83	80	80
3		65	54	n.d.
4		47	42	n.d.
5		35	28	n.d.
6		25	19	n.d.
7		65	61	n.d.

[a] Reaction conditions: amide (0.5 mmol), complex (**3**) (0.005 mmol, 1.0 mol%, 2.21 mg), KOtBu (0.05 mmol, 10 mol%, 2.8 mg), dry isopropanol (2 ml), H2 (50 bar) at 150 °C, 18 h. Pressure of hydrogen at room temperature. [b] Conversion and yields were calculated by GC using hexadecane as external standard. (n.d. = not detected).

CONCLUSIONS

In conclusion, we have synthesised two novel ruthenium pincer complexes bearing an imidazolylaminophosphino ligand. The BH_4-substituted derivative **3** constitutes an efficient catalyst for the hydrogenolysis of different substituted amides to the corresponding alcohols and amines without base under comparably ~~mild~~ conditions. Less reactive aliphatic and aromatic primary amides have been successfully reduced with such system for the first time. Interestingly, the novel catalyst possesses a modular structure by virtue of which its electronic and steric properties can be easily modified. In this respect, the preparation of a small library of new complexes is underway in our group.

EXPERIMENTAL SECTION

Synthesis of 3-(di-*tert*-butylphosphino)-N-((1-methyl-1H-imidazol-2-yl)methyl)propylamine (1).

A solution of 3-(di-*tert*-butylphosphino)propylamine (500 mg, 2.46 mmol, 1 eq.) in 10 mL methanol was added dropwise to a solution of 1-methyl-1H-imidazole-2-carbaldehyde (271 mg, 2.46 mmol, 1 eq.) in 10 mL methanol. The resulting solution was stirred at room temperature for 24 hours. It was then cooled to 0 °C with a water/ice bath and sodium borohydride (139 mg, 3.70 mmol, 1.5 eq.) added in one portion. The resulting solution was stirred at room temperature for 24 hours. The solvent was then removed under reduced pressure and the oily residue partitioned between 20 mL dichloromethane and 20 mL of distilled water. The organic phase was separated and the aqueous phase further extracted with dichloromethane (2 x 10 mL). The collected organic phases were dried over sodium sulfate and then filtered through a short pad of basic alumina. The solvent was removed under reduced pressure to leave 3-(di-*tert*-butylphosphino)-*N*-((1-methyl-1H-imidazol-2-yl)methyl)propylamine **1** as a very faint yellow liquid. The compound was 89% pure according to ^{31}P NMR (yield 89%) and was used as such for the next step.

^{1}H{^{31}P} NMR (400 MHz, DCM-d_2) δ 6.89-6.85 (m, 2H, C$\underline{H}_{Im}$), 3.82 (s, 2H, Im-C$\underline{H}_2$), 3.68 (s, 3H, NC$\underline{H}_3$), 2.73 (t, J = 7.0 Hz, 2H, HN(C$\underline{H}_2$)), 1.71 – 1.61 (m, 2H, C$\underline{H}_2$), 1.54 (b, 1H, N$\underline{H}$), 1.41-1.36 (m, 2H, (C$\underline{H}_2$)P), 1.09 (s, 9H, C(C$\underline{H}_3$)$_3$). **^{1}H NMR** (400 MHz, DCM-d_2) δ 1.14 (d, J_{HP} = 10.7 Hz, 9H, C(C$\underline{H}_3$)$_3$). **^{13}C NMR** (101 MHz, DCM-d_2) δ 147.30 (s, $\underline{C}_{Im}$), 127.11 (s, $\underline{C}H_{Im}$), 121.41 (s, $\underline{C}H_{Im}$), 51.34 (d, J_{CP} = 13.8 HN(C$\underline{H}_2$)), 46.28 (s, Im-C$\underline{H}_2$), 32.95 (s, NC$\underline{H}_3$), 31.41 (d, J_{CP} = 21.2 Hz, $\underline{C}$(CH$_3$)$_3$), 31.24 (d, J_{CP} = 25.2 Hz, $\underline{C}H_2$), 29.78 (d, J_{CP} = 13.6 Hz, C($\underline{C}$H$_3$)$_3$), 19.02 (d, J_{CP} = 21.0 Hz, ($\underline{C}$H$_2$)P).**^{31}P{^{1}H}** NMR (162 MHz, DCM-d_2) δ 28.71 (s).

Synthesis of {Ru(H)(Cl)(CO)(3-(di-*tert*-butylphosphino)-N-((1-methyl-1H-imidazol-2-yl)methyl)-propylamine)} (2).

To a suspension of {Ru(H)(Cl)(CO)(PPh$_3$)$_3$} (1.39 g, 1.46 mmol, 1 eq.) in toluene (10 mL) was added 3-(di-*tert*-butylphosphino)-*N*-((1-methyl-1H-imidazol-2-yl)methyl)propylamine) **1** (478 mg, 1.61 mmol, 1.1 eq). The suspension was refluxed for 3 hours. During this time, the reaction mixture turned into a suspension of a white solid in a yellow solution. After being cooled down, the suspension was filtered with the aid of a sintered glass frit and the solid rinsed several times with diethyl ether. The product was obtained as an off-white solid (601 mg, 89% yield).The complex is obtained as a mixture of two isomers, *syn*-**2** (74%) and *anti*-**2** (26%).

NMR spectra were recorded in DCM-d$_2$. However in this solvent, the complex is not indefinitely stable as the hydride is slowly replaced by chloride.

Syn-2 74%

^{1}H{^{31}P} NMR (400 MHz, DCM-d_2) δ 7.15 (t, J = 1.2 Hz, 1H, =NC$\underline{H}_{Im}$=), 6.90 (bs, 1H, MeNC$\underline{H}_{Im}$=), 4.23 (dd, J = 14.7, 5.2 Hz, 1H, Im-C$\underline{H}_2$), 4.05 (bt, 1H, N$\underline{H}$), 3.60 (s, 3H, NC$\underline{H}_3$), 3.58 (dd, J = 14.7, 11.2 Hz, 1H, Im-C$\underline{H}_2$), 3.31 (ddd, J = 11.7,

5.6, 3.5 Hz, 1H, HN(C$\underline{H}_2$)), 2.66 – 2.48 (m, 1H, HN(C$\underline{H}_2$)), 2.24 – 2.15 (m, 1H, C$\underline{H}_2$), 2.06 (ddd, *J* = 14.9, 5.7, 1.8 Hz, 1H, (C$\underline{H}_2$)P), 1.96 (m, 1H, C$\underline{H}_2$), 1.44 (s, 9H, C(C$\underline{H}_3$)$_3$), 1.36 (m, 1H, (C$\underline{H}_2$)P, overlapped by C(C$\underline{H}_3$)$_3$ signals), 1.25 (s, 9H, C(C$\underline{H}_3$)$_3$), -15.91 (s, 1H, Ru$\underline{H}$). **^{1}H NMR** (400 MHz, DCM-d_2) δ 1.44 (d, J_{HP} = 12.6 Hz, 9H, C(C$\underline{H}_3$)$_3$), 1.25 (d, J_{HP} = 12.3 Hz, 9H, C(C$\underline{H}_3$)$_3$), -15.91 (d, J_{HP} = 25.2 Hz, 1H, Ru$\underline{H}$). **^{13}C NMR** (101 MHz, DCM-d_2) δ 208.17 (d, J_{CP} = 17.8 Hz, $\underline{C}$O), 145.22 (s, $\underline{C}_{Im}$), 128.55 (s, =N$\underline{C}$H$_{Im}$=), 122.34 (s, MeN$\underline{C}$H$_{Im}$=), 55.63 (s, HN($\underline{C}$H$_2$)), 51.27 (s, Im-C$\underline{H}_2$), 38.44 (d, J_{CP} = 15.0 Hz, $\underline{C}$(CH$_3$)$_3$), 35.75 (d, J_{CP} = 27.0 Hz, $\underline{C}$(CH$_3$)$_3$), 34.54 (s, N$\underline{C}$H$_3$), 30.38 (bs, C($\underline{C}$H$_3$)$_3$), 30.22 (d, J_{CP} = 4.1 Hz, C($\underline{C}$H$_3$)$_3$), 26.64 (d, J_{CP} = 3.4 Hz, $\underline{C}$H$_2$), 20.33 (d, J_{CP} = 15.9 Hz, ($\underline{C}$H$_2$)P). **^{31}P{^{1}H}** NMR (162 MHz, DCM-d_2) δ 78.11 (s).

Anti-2 26%

^{1}H{^{31}P} NMR (400 MHz, DCM-d_2) δ δ7.15 (m, 1H, =NC$\underline{H}_{Im}$=, overlapped by same signal from major isomer), 6.89 (bs, 1H C$\underline{H}_{Im}$), 3.92 (d, *J* = 13.9 Hz, 1H, C$\underline{H}_2$), 3.59 (s, 3H, NC$\underline{H}_3$), 2.99 – 2.80 (m, 1H, C$\underline{H}_2$), 1.81 – 1.66 (m, 1H, C$\underline{H}_2$), 1.34 (s, 9H, C(C$\underline{H}_3$)$_3$), 1.31 (s, 9H, C(C$\underline{H}_3$)$_3$), -16.25 (bs, 1H, Ru$\underline{H}$). **^{1}H NMR** (400 MHz, DCM-d_2) δ 1.34 (d, J_{HP} = 11.3 Hz, 9H, C(C$\underline{H}_3$)$_3$), 1.31 (d, J_{HP} = 12.2 Hz, 9H, C(C$\underline{H}_3$)$_3$), -16.25 (bd, J_{HP} = 23.0 Hz, 1H, Ru$\underline{H}$). **^{31}P{^{1}H}** NMR (162 MHz, DCM-d_2) δ 74.19 (s).

IR ATR: ῡ [cm^{-1}] 1890 (s, ν CO).

ESI-HRMS (m/z, pos): Calculated for [C17H32ClN3OPRu] 462.10108; found: 462.10123 [M-H]$^+$.

Synthesis of {Ru(H)(BH$_4$)(CO)(3-(di-*tert*-butylphosphino)-N-((1-methyl-1H-imidazol-2-yl)methyl)-propylamine)} (3).

To a solution of {Ru(H)(Cl)(CO)(3-(di-*tert*-butylphosphino)-*N*-((1-methyl-1H-imidazol-2-yl)methyl)-propylamine)} **2** (360 mg, 0.78 mmol, 1 eq.) was added sodium borohydride (441 mg, 11.66 mmol, 15 eq.). The flask was immersed in a preheated oil bath (set temperature 90 °C) and refluxed for 30 minutes. After this time, the solution was stirred at room temperature for 24 hours. The solvents were removed under reduced pressure and the residue partioned between 35 mL water and 35 mL dichloromethane. The organic phase was separeted and the aqueous phase further extracted with dichloromethane (2x15 mL). The collected organic phases were dried over sodium sulfate. The solution was filtered with the aid of a sintered glass frit. The solvent was removed under reduced pressure. The solid was then washed with diethyl ether until the surnatant solution was no longer yellowish and became colorless. The solvent was removed under reduced pressure to leave an off-white solid. Isolated yield: 78% (270 mg). The complex was obtained as a mixture of two isomers in a a 90:10 ratio.

(3) proved poorly soluble in various solvents. Solubility in tetrahydrofurane allows for a good signal to noise ratio. However in this solvent, the complex is not indefinitely stable and it slowly decomposes.

Major isomer

^{1}H{^{31}P} NMR (400 MHz, THF-d_8) δ 7.02 (d, *J* = 1.5 Hz, 1H, =NC$\underline{H}_{Im}$=), 6.93 (d, *J* = 1.5 Hz, 1H, MeNC$\underline{H}_{Im}$=), 4.69 (bt, 1H, N$\underline{H}$), 4.30 (dd, *J* = 14.5, 5.0 Hz, 1H, Im-C$\underline{H}_2$), 3.61 (s, 3H, NC$\underline{H}_3$), 3.46 (dd, *J* = 14.5, 11.2 Hz, 1H, Im-C$\underline{H}_2$), 3.31 (ddt, *J* = 10.6, 8.1, 4.1 Hz, 1H, HN(C$\underline{H}_2$)), 2.47 (bq, *J* = 11.5 Hz, 1H, HN(C$\underline{H}_2$)), 2.17 – 2.06 (m, 1H, C$\underline{H}_2$), 2.01 (ddd, *J* = 14.8, 5.5, 1.9 Hz, 1H, (C$\underline{H}_2$)P), 1.86 (ddd, *J* = 14.9, 13.1, 11.3 Hz, 1H, C$\underline{H}_2$), 1.43 (dd, *J* = 12.1, 10.3 Hz, 1H, (C$\underline{H}_2$)P), 1.37 (s, 9H, C(C$\underline{H}_3$)$_3$), 1.28 (s, 9H, C(C$\underline{H}_3$)$_3$), -1.83 (unresolved q, *J* = 102.7 Hz, 4H, B$\underline{H}_4$), -13.00 (s, 1H, Ru$\underline{H}$). **^{1}H NMR** (400 MHz, THF-d_8) δ 1.37 (d, J_{HP} = 12.4 Hz, 9H, C(C$\underline{H}_3$)$_3$), 1.28 (d, J_{HP} = 12.2 Hz, 9H, C(C$\underline{H}_3$)$_3$), -13.00 (d, J_{HP} = 22.7 Hz, 1H, Ru$\underline{H}$). **^{13}C NMR** (101 MHz, THF-d_8) δ 208.32 (d, J_{CP} = 18.0 Hz, $\underline{C}$O), 145.92 (s, $\underline{C}_{Im}$), 129.33 (s, =N$\underline{C}$H$_{Im}$=), 121.91 (s, MeN$\underline{C}$H$_{Im}$=), 55.77 (s, HN($\underline{C}$H$_2$)), 51.62 (s, Im-C$\underline{H}_2$), 38.40 (d, J_{CP} = 16.5 Hz, $\underline{C}$(CH$_3$)$_3$), 35.83 (d, J_{CP} = 25.4 Hz, $\underline{C}$(CH$_3$)$_3$), 33.83 (s, N$\underline{C}$H$_3$), 30.59 (s, C($\underline{C}$H$_3$)$_3$), 30.15 (d, J_{CP} = 4.4 Hz, C($\underline{C}$H$_3$)$_3$), 27.00 (d, J_{CP} = 3.4 Hz, $\underline{C}$H$_2$), 20.82 (d, J_{CP} = 3.4 Hz, ($\underline{C}$H$_2$)P). **^{31}P{^{1}H}** NMR (162 MHz, THF-d_8) δ 82.44 (s). **^{11}B{^{1}H}** NMR (96 MHz, THF-d_8) δ -26.55 (bs).

Minor isomer

^{1}H{^{31}P} NMR (400 MHz, THF-d_8) δ 7.04 (d, *J* = 1.4 Hz, 1H, C$\underline{H}_{Im}$), 6.94 (d, *J* = 1.4 Hz, 1H, C$\underline{H}_{Im}$), 4.11 (dd, *J* = 14.3, 10.8 Hz, 1H, C$\underline{H}_2$), 3.91 (dd, *J* = 14.4, 5.8 Hz, 1H, C$\underline{H}_2$), 3.77 (d, *J* = 8.7 Hz, 1H, C$\underline{H}_2$), 2.99-2.93 (bm, 1H, C$\underline{H}_2$), 1.34 (s, 9H, C(C$\underline{H}_3$)$_3$), -13.52 (s, 1H, Ru$\underline{H}$). **^{1}H NMR** (400 MHz, THF-d_8) δ -13.52 (d, J_{HP} = 19.6 Hz, 1H, Ru$\underline{H}$). **^{31}P{^{1}H}** NMR (162 MHz, THF-d_8) δ 79.59 (s). **^{11}B{^{1}H}** NMR (96 MHz, THF-d_8) δ -31.51 (bs).

IR ATR: ῡ [cm^{-1}] 2344 (ν BH$_t$), 1905 (s, ν CO, BH$_b$).

ESI-HRMS (m/z, pos): Calculated for [C17H33N3OPRu] 428,14039; found: 428,14056 [M-BH$_4$]$^+$.

General procedure for the hydrogenation of amides with ruthenium complexes without added base.

A 4 mL glass vial containing a stirring bar was sequentially charged with the corresponding amide (0.5 mmol) and the corresponding amount of ruthenium complex **2** or **3** (0.25-2 mol%). Afterwards, the reaction vial was capped with a septum equipped with a disposable syringe needle and set in the alloy plate and the vial was purged with three cycles of vacuum/argon and argon atmosphere was established. Then, dry isopropanol (2 ml) was added under argon and the vials were then placed into a 300 mL autoclave. Once sealed, the autoclave was purged three times with 30 bar of hydrogen, then pressurized to the desired hydrogen pressure (15, 30 or 50 bar) and placed into an aluminium block which was preheated to the desired temperature (80-150 °C). After the desired reaction time (3-18 h), the autoclave was cooled in an ice bath and the remaining gas was carefully released. Finally, *n*-hexadecane (50 mg) was added as an external standard, the reaction mixture was diluted with ethyl acetate and analysed by GC.

General procedure for the hydrogenation of amides with ruthenium complexes and base.

A 4 mL glass vial containing a stirring bar was sequentially charged with the corresponding amide (0.5 mmol) and the corresponding amount of ruthenium complex **2** or **3** (0.25-2 mol%). Afterwards, the reaction vial was capped with a septum equipped with a disposable syringe needle and set in the alloy plate and the vial was purged

with three cycles of vacuum/argon and argon atmosphere was established. Then, dry isopropanol (1 ml) and the corresponding amount of KO^{t}Bu (1-10 mol%) previously dissolved in dry isopropanol (1 ml) were sequentially added under argon and the vials were then placed into a 300 mL autoclave. Once sealed, the autoclave was purged three times with 30 bar of hydrogen, then pressurized to the desired hydrogen pressure (15, 30 or 50 bar) and placed into an aluminium block which was preheated to the desired temperature (80-150 °C). After the corresponding reaction time 3-18 h, the autoclave was cooled in an ice bath and the remaining gas was carefully released. Finally, *n*-hexadecane (50 mg) was added as an external standard, the reaction mixture was diluted with ethyl acetate and analysed by GC.

ASSOCIATED CONTENT

Supporting Information. General information concerning synthesis and hydrogenation reactions, NMR and IR spectra of **1**, **2** and **3**, crystal data of *syn*-**2**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Funding Sources

The authors would like to thank the ACS Pharmaceutical Roundtable for financial support and its members, especially Dr. Fabrice Gallou, for fruitful scientific discussions. In addition, support by the state of Mecklenburg-Vorpommern and the BMBF are acknowledged. J.R.C.-A. thanks the Ramon Areces Foundation for a postdoctoral fellowship.

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(16) Crystal data for *syn*-**2**: $C_{17}H_{33}N_3OPRu$, M = 462.95, monoclinic space group $P2_1/c$ (no. 14), a = 13.505(3), b = 12.224(2), c = 15.157(3) Å, β = 105.990(3)°, V = 2271.9(9) Å^3, T = 150.(2) K, Z = 4, ρcalcd = 1.353 g cm^{-3}, μ(Mo Kα) = 0.887 mm^{-1}. 31730 total data, Θ_{max} = 26.00°. 4468 independent reflections (R_{int} = 0.0348), R = 0.0227 for 3948 unique data with $I > 2\sigma(I)$ and 232 refined parameters. The final R_1 values were 0.0260 (all data). The final $wR(F^2)$ values were 0.0612 (all data). The goodness of fit on F^2 was 1.055. Crystallographic data (excluding structure factors) for the structures reported in this paper have been deposited at the Cambridge Crystallographic Data Centre as supplementary publication no. CCDC-1404520 for *syn*-**2**. Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge, CB21EZ, UK (fax: int. code + (1223) 336-033; e-mail: deposit@ccdc.cam.ac.uk.

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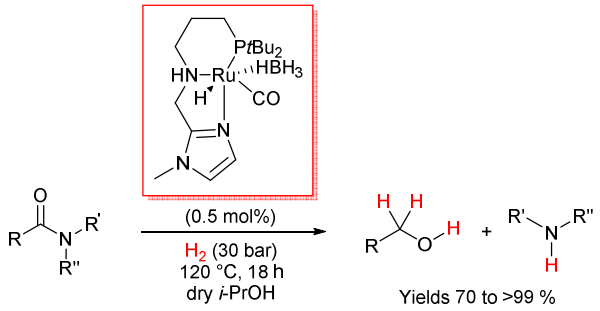

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