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Hydrogenation of Carbonyl Derivatives with Well-Defined Rhenium Pre-Catalyst

Duo Wei,[a] Thierry Roisnel,[a] Christophe Darcel,[a] Eric Clot[b] and Jean-Baptiste Sortais*[a]

Dedication ((optional))

Abstract: The first efficient and general rhenium catalyzed hydrogenation of carbonyl derivatives has been developed. The key to success of the reaction is the use of a well-defined rhenium complex bearing a tridentate diphosphino-amino ligand as catalyst (0.5 mol%) at 70 °C in the presence of H_2 (30 bar). The mechanism of the reaction has been investigated by DFT(PBE0-D3) calculations.

Hydrogenation reactions have been of central importance in chemistry for more than a century.[1] Nevertheless, it remains an important field of investigation, notably with the current challenge of the transformation of highly oxygenated biomass-resources into less functionalized chemical building blocks.[2] Compared to the transition metals of groups 8, 9, and 10 (Fe, Co, Ni) which are classical in reduction area, group 7 transition metals have been scarcely applied in hydrogenation or related reduction reactions.[3] For example, with manganese, only one recent article describes the hydrogenation of carbonyl derivatives[4] and one the dehydrogenative coupling of alcohol with amines.[5] In the case of rhenium, after the seminal work of Ephritikhine on dehydrogenation of alkanes to alkenes,[6] rare examples of stoichiometric[7] and catalytic[8] hydrogenation of alkenes have been described with rhenium nitrosyl hydride complexes mainly by Berke, and a single example of the hydrogenation of acetophenone is reported.[8b] Interestingly, Berke has also developed a bifunctional rhenium complex, bearing a non-innocent cyclopentadienol ligand, as hydrogen transfer catalysts for the reduction of ketones and imines.[8f, 9] Due to the importance of cooperative metal-ligand complexes in hydrogenation,[10] notably through the so-called NH-effect,[11] we became interested in the preparation of well-defined rhenium PN(H)P pincer complexes as catalysts for reduction reactions. We report herein the first efficient and broad scope hydrogenation of carbonyl derivatives with a well-defined rhenium complex based on a PN(H)P ligand.

Until now, rhenium PNP pincer type complexes have been sparsely discussed in the literature.[8f, 12]. To start our study, we have selected commercially available $Re(CO)_5Br$ as metal precursor and $NH(CH_2CH_2P(iPr)_2)_2$ as ligand. Upon stoichiometric reaction in toluene at 100 °C, the air-stable cationic tricarbonyl rhenium bromide complex **1** was conveniently prepared in a straightforward manner and high yield (92%, Figure 1). The resulting white complex was fully characterized by NMR spectroscopy, mass and elemental analysis. The molecular structure of this complex was also confirmed by X-ray diffraction analysis. Surprisingly, in the solid state, as well as in solution, the ligand adopts a facial coordination at Re contrary to other octahedral complexes with Mn,[4] Fe,[13] Ru[14] or Os[15] that exhibit a meridional coordination mode of the ligand.

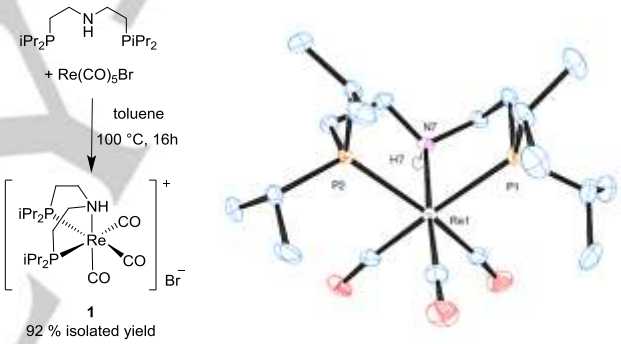

Figure 1. Synthesis and ORTEP view of the molecular structure of the rhenium complex **1.**

Our initial investigations, aiming at probing the hydrogenation catalytic activity of **1**, were carried out on acetophenone **a1** (Table 1). Full reduction of **a1** to the corresponding 1-phenylethanol **b1** was achieved in the presence of 5 mol% of complex **1,** 10 mol% *t*-BuOK , 50 bar of H_2 at 110 °C for 16 h (entry 1). Interestingly, these conditions resulted in full conversion already after 2 hours (entry 2). Using only $Re(CO)_5Br$, without any ligand, resulted in no hydrogenation activity (entry 3). The same lack of reactivity was also observed in the absence of base (entry 4). The influence of reaction parameters such as temperature, catalyst loading and pressure was investigated. At 70 °C, full conversion of **a1** was still observed after 16 hours (entry 5), but lowering the temperature to 30 °C completely shuts down catalytic activity (entry 6). Under 50 bar of H_2, at 70 °C, the catalyst loading could be decreased to 0.5 mol% without losing any activity, however, with only 0.1 mol% of **1**, the conversion dropped to 63% (TON 630, entries 7-8). The pressure of hydrogen can be lowered to 30 bar in the presence of 0.5 mol% of catalyst (entry 9). Ketone hydrogenation still takes place with lower pressure, down to 1 bar, even with a balloon of H_2, although at the expense of the charge of catalyst and temperature (entries 10-12). The optimal

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conditions selected to probe the substrate scope of the reaction are 0.5 mol% of **1**, 1.0 mol% of base, 30 bar of H_2, 70 °C for 16 hours (Figure 2).

Table 1. Optimization of the reaction parameters[a].

Entry	Complex (mol%)	*t*-BuOK (mol%)	H_2 (bar)	T (°C)	t (h)	NMR yield (%)
1	**1** (5)	10	50	110	16	> 98
2	**1** (5)	10	50	110	2	> 98
3	$Re(CO)_5Br$ (5)	10	50	110	2	< 3
4	**1** (5)	-	50	110	2	< 3
5	**1** (5)	10	50	70	16	> 98
6	**1** (5)	10	50	30	16	< 3
7	**1** (0.5)	1	50	70	16	> 98
8	**1** (0.1)	5	50	70	18	63
9	**1** (0.5)	1	30	70	16	> 98
10	**1** (1)	2	10	70	18	90
11	**1** (5)	10	1	110	16	85
12	**1** (5)	10	1[b]	110	16	81

[a] Reaction conditions: in a glove box, an autoclave is filled with 1) complex **1**, 2) toluene, 3) acetophenone **a1** 4) *t*-BuOK, then pressurized with H_2. The reaction is heated in an oil bath. [b] A balloon of H_2 was used.

In general, electron-donating and electron-withdrawing substituents, e.g. *o*- and *p*-methyl (**b2**, **b3**), *p*- and *o*-methoxy (**b4**, **b5**), *p*-morpholinyl (**b7**), *p*-fluoro (**b11**), *p*- and *o*-chloro (**b12**, **b13**), *p*-bromide (**b16**, **b20**), *p*-trifluoromethyl (**b8**), *p*-amino (**b10**) and the more reactive *p*-iodo (**b14**) groups are well tolerated. Harsher conditions were needed for the hydrogenation of *o*-methoxy-acetophenone (**a5**). In addition, 2'-acetonaphthone (**a6**) and di-ketones (**a10**) gave also good yields. Next, we explored the activity of the rhenium catalyst towards a collection of more sterically hindered ketones (**a15**-**20**, **a23**, **a24**). As an example, pivalophenone (**a19**) was successfully hydrogenated to the corresponding alcohol (**b19**) in 72% isolated yield. 1-Indanone (**a21**), α-tetralone (**a22**) could be converted to alcohols at 110 °C. Noteworthy, the α,β-unsaturated chalcone afforded selectively the saturated alcohol (**b25**) in good yield, and the reduction of benzylideneacetone (**b26**) led to 4-phenylbutan-2-ol as the major product, contaminated with unsaturated alcohol (ratio 90 : 10). Additionally, the heteroaromatic substrates (**a27-34**) based on thiophene, furane, pyridine, pyrole and thiazole were smoothly converted into alcohols.

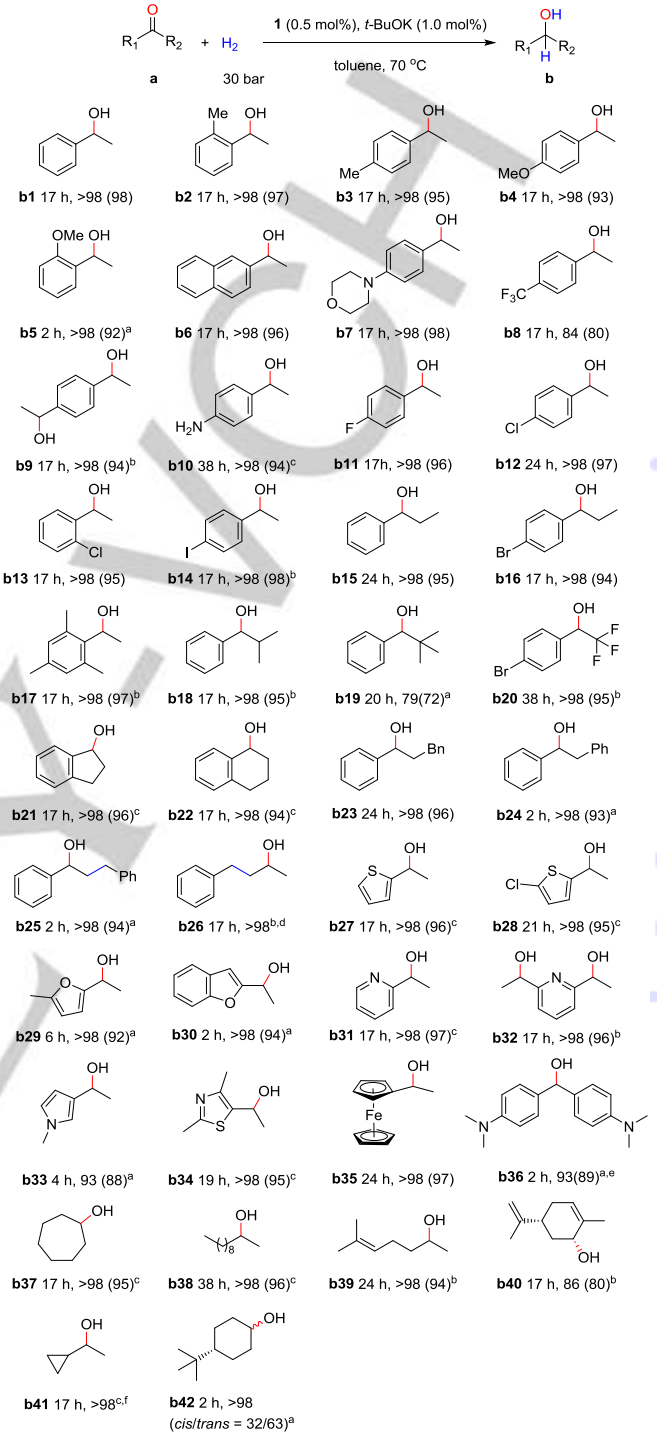

Figure 2. Scope of the hydrogenation of ketones to give alcohols under the catalysis of $[Re(NH(CH_2CH_2P(iPr_2)_2)(CO)_3]Br$. (General conditions: ketone (2.5 mmol), H_2 (30 bar), **1** (0.5 mol%), *t*-BuOK (1.0 mol%), toluene, 70 °C; Isolated yields in parentheses; [a] H_2 (50 bar), **1** (5.0 mol%), *t*-BuOK (10 mol%), 110 °C; [b] H_2 (50 bar), **1** (1.0 mol%), *t*-BuOK (2.0 mol%), 110 °C; [c] H_2 (30 bar), **1** (0.5 mol%), *t*-BuOK (1.0 mol%), 110 °C; [d] 10% of the unsaturated alcohol was detected in the crude mixture; [e] Isolated yield with 3 % of starting material; [f] THF as solvent.)

Even the difficult di(*p*-dimethylaminophenyl)methanone **a36** can be hydrogenated with this catalytic system. Then, we explored the

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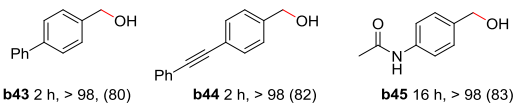
scope of aliphatic ketones (**a37-42**). Under these conditions the rhenium-based catalyst tolerates cyclic, long-chain and remote C=C bond (**b39, b40**). Starting from the enantiopure (*R*)-carvone **a40**, (-)-*cis*-carveol is obtained as a single diastereoisomer **b40.** Besides, the internal tri-substituted conjugated C=C in **a40** is not reduced. Notably, the cyclopropyl-substituted ketone furnished a quantitative yield of **b41** indicating that the reaction does not proceed via stable radical intermediates. Hydrogenation of 4-(*tert*-butyl)cyclohexanone **a42** gave a full conversion with a *cis*/*trans* ratio of 32/63.



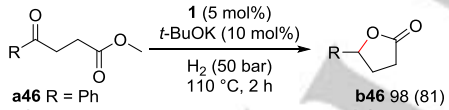
b43 2 h, > 98, (80) **b44** 2 h, > 98 (82) **b45** 16 h, > 98 (83)

Figure 3. Scope of the hydrogenation of aldehydes to give alcohols under the catalysis of [Re(NH($CH_2CH_2P(iPr_2)_2$)$(CO)_3$]Br. General conditions: H_2 (50 bar), **1** (5.0 mol%), *t*-BuOK (10 mol%), 110 °C, toluene.

Aldehydes can also be reduced to the corresponding alcohols with this catalytic system (Figure 3). For example, 4-biphenylaldehyde **b43** was hydrogenated to the corresponding primary alcohol smoothly in 2 h. Internal C-C triple bond and amide were tolerated (**b44**-**b45**).

Finally, despite this significant scope and functional group tolerance, a few limitations also need to be noted. No conversion was detected with substrates containing coordinating cyano group, acidic phenolic and boric acid on the aromatic ring as well as chelating β-ester and β-acetyl substituents.

Next, γ-keto-esters, such as methyl 3-benzoylpropionate **a46** were subjected to the reductive conditions in the presence of **1**. To our delight γ-phenyl γ-butyrolactone **b46** was obtained in high conversion/yield, showing the tolerance toward ester/lactone functional groups. Interestingly, starting from the biomass derived ethyl levunilate **a47**, γ-valerolactone **b47**, which can be used as liquid fuel, additive, solvent or intermediate for organic synthesis,[16] was obtained in good yield (78%) using standard conditions, *i.e.* 5 mol% of **1**, 50 bar of H_2, at 110 °C for 2 h (Figure 4).[17]



a46 R = Ph
a47 R = Me

b46 98 (81)
b47 82 (78)

Figure 4. Synthesis of γ-lactones from γ-keto-esters. Isolated yield in parentheses.

On the basis of previous works of other groups on related complexes with Fe and Ru,[18] as well as our DFT(PBE0-D3) calculations,[19] we propose the following mechanism (Figure 5). In a first step, the base activates the precatalyst **1** by exoergic deprotonation of the NH moieties to form **2** (ΔG = -46.6 kcal mol^{-1}), followed by the isomerisation to the more stable *mer*-[Re(P(N)P)$(CO)_3$] complex **3** (ΔG = -3.9 kcal mol^{-1}). Dissociation of CO from **3** is slightly uphill (ΔG = 6.3 kcal mol^{-1}) and forms the 16-electron dicarbonyl complex **4** that is the active form of the catalyst. Endoergic coordination of H_2 to form **5** (ΔG = 20.5 kcal mol^{-1}) is followed by facile heterolytic splitting of dihydrogen ($\Delta G^{\#}$ = 5.1 kcal mol^{-1}) to yield the amino-hydride intermediate **6**, only slightly less stable than **4** (ΔG = 1.9 kcal mol^{-1}). Acetophenone forms an adduct with **6** essentially upon interaction of the carbonyl oxygen with the N-H proton (ΔG = 6.5 kcal mol^{-1}). The carbonyl reduction is a two-steps process with first hydride transfer from Re to C ($\Delta G^{\#}$ = 13.5 kcal mol^{-1} and ΔG = 10.5 kcal mol^{-1}), followed by proton transfer from N-H to O, regenerating the active species **4**.[20] Overall, the rate-determining step is the H_2 heterolytic splitting with an activation barrier of $\Delta G^{\#}$ = 31.9 kcal mol^{-1} from **3**. Kinetic modelling with Copasi[21] using the calculated activation barriers indicated that, with 0.5 mol% of **3** and an equimolar ratio of acetophenone and H_2, the yield in alcohol after 20 hours is only *ca.* 5%. Increasing the ratio of H_2 with respect to ketone to 10:1 resulted in an increased conversion of *ca.* 50% after 20 hours. Full conversion was obtained in *ca.* 20 hours when the initial ratio was 20:1 in favour of dihydrogen.[22] This qualitatively shows the importance of using significantly high pressure of H_2 and good stirring to facilitate the energy-demanding first step of the reaction by increasing the concentration of H_2.

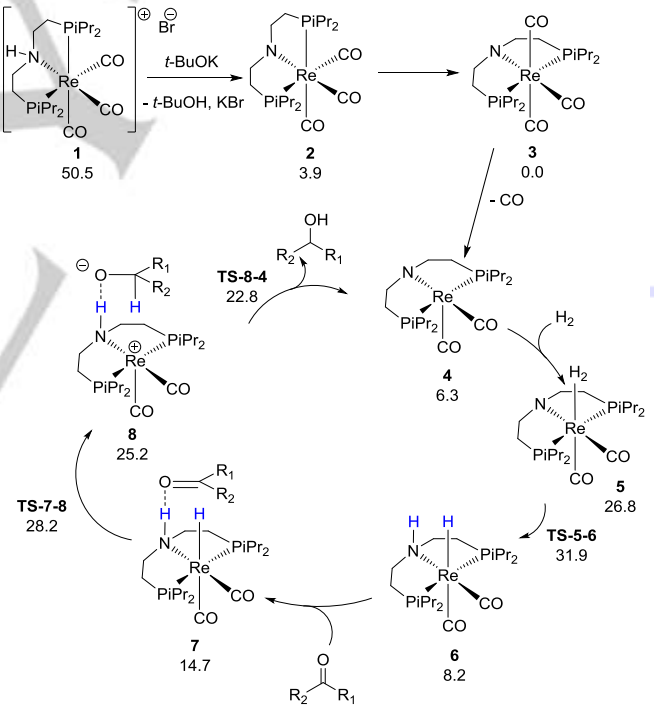


Figure 5. Proposed catalytic cycle for the rhenium hydrogenation of ketones to give alcohols based on PBE0-D3 calculations. DFT computed Gibbs free energies (kcal mol-1) relative to **3** are shown.

In conclusion, we have developed an efficient and general hydrogenation of carbonyl derivatives using a well-defined rhenium PN(H)P complex **1**. Of notable interest, the reduction proceeds well for a large range of substrates with low catalyst loading (0.5 mol%) under mild conditions (70 °C) and 30 bar of H_2.

Experimental Section

Complex 1. Bis[(2-di-isopropylphosphino)ethyl]amine (0.492 mmol, 1.7 mL, 10 wt% in THF, 1.0 equiv.) was added to a solution of $Re(CO)_5Br$ (0.492 mmol, 200 mg 1.0 equiv.) in toluene (8 mL). The mixture was stirred at 100 °C for 18 h. Toluene was then evaporated. The crude residue was then recrystallized from dichloromethane and pentane to afford white needle crystals (297 mg, 92%). Complete details of the X-ray analyses reported herein have been deposited at the Cambridge Crystallographic Data Center (CCDC 1501902). **Typical catalytic hydrogenation**. In an argon filled glove box, an autoclave was charged with complex **1** (8.2 mg, 0.5 mol%) and toluene (2.5 mL), followed by ketone (2.5 mmol) and *t*-BuOK (2.8 mg, 1.0 mol%), in this order. The autoclave is then charged H_2 (30 bar). The mixture was stirred for 17 h at 70 °C in an oil bath.

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Keywords: Rhenium • hydrogenation• ketones • mechanism • DFT-D3 calculations

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[22] See S.I. for details.

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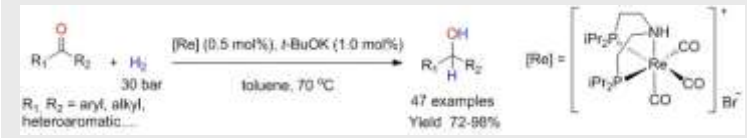

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Hydrogenation of Carbonyl Derivatives with Well-Defined Rhenium Pre-Catalyst

An efficient and general rhenium catalyzed hydrogenation of carbonyl derivatives has been developed based on a well-defined rhenium complex bearing a tridentate diphosphino-amino ligand. The mechanism of the reaction has been investigated by DFT (PBE0-D3) calculations.