Catalytic Hydrogenation

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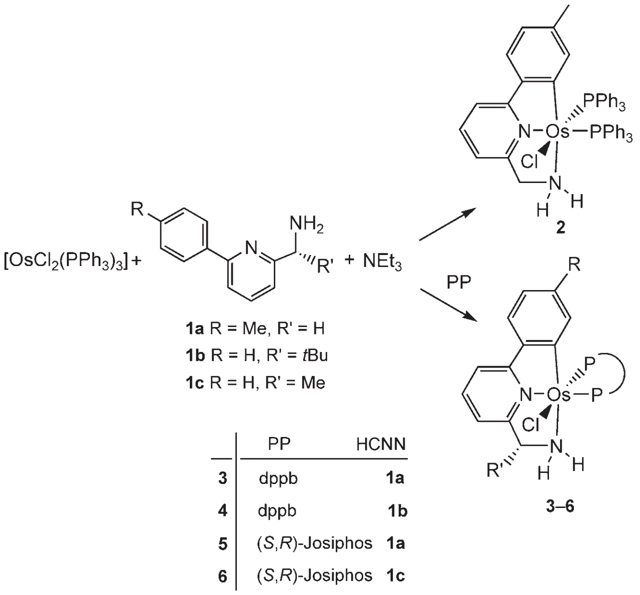
Osmium(II) CNN Pincer Complexes as Efficient Catalysts for Both Asymmetric Transfer and H_2 Hydrogenation of Ketones**

Walter Baratta, Maurizio Ballico, Giorgio Chelucci, Katia Siega, and Pierluigi Rigo*

Catalytic asymmetric hydrogenation (HY) and transfer hydrogenation (TH) of carbonyl compounds are usually performed with Ru, Rh, and Ir complexes,[1] and much less attention has been devoted to other transition-metal based-systems. Although osmium complexes have occasionally been employed in the HY[2] and TH[3] of carbonyl compounds, we have recently shown that $[OsCl_2P_2(Pyme)]$[4a] [P_2 = diphosphane; Pyme = 1-(pyridin-2-yl)methanamine)] complexes are extremely active catalysts in the TH of ketones, with reaction rates comparable to those of their Ru analogues.[4b] Owing to the stronger bonding of Os compared to Ru, robust and thermally stable chiral complexes can be obtained using a suitable set of ligands, which is a crucial breakthrough in achieving catalysts that display high productivity.[5] Since the CNN pincer complexes $[RuCl(CNN)P_2]$[6] obtained from 1-(6-arylpyridin-2-yl)methanamines (HCNN) are among the most active catalysts for the TH of carbonyl compounds, we decided to investigate the chemistry of osmium complexes with CNN ligands and report herein the isolation of the first CNN pincer osmium derivatives $[OsCl(CNN)P_2]$. These complexes are extremely active and productive catalysts for both the TH and HY of ketones (turnover frequency (TOF) of up to $1.3\times10^6\ h^{-1}$). Moreover, asymmetric TH[7] and HY[1] have been achieved (*ee* values of up to 98%) with a remarkably low loading (0.005–0.002 mol%) of the chiral version of these pincer complexes. Finally, the reversible nature of the ketone insertion into the Os–H bond suggests that Os-hydride and Os-alkoxide species are involved in TH and HY.

Treatment of $[OsCl_2(PPh_3)_3]$ with **1a** (1.2 equiv) in 2-propanol in the presence of the weak base NEt_3 at reflux for 2 h affords the CNN pincer complex **2**[8] in 94% yield (Scheme 1). The ^{31}P NMR spectrum of **2** shows two doublets at $\delta = 7.1$ and -1.6 ppm with a $^2J_{P,P}$ coupling constant of 15.7 Hz, which is typical for a *cis* OsP_2 arrangement. The singlet at $\delta = 7.95$ ppm in the ^1H NMR spectrum is due to the CH proton close to the orthometalated carbon.



	PP	HCNN
3	dppb	1a
4	dppb	1b
5	(*S*,*R*)-Josiphos	1a
6	(*S*,*R*)-Josiphos	1c

Scheme 1. Synthesis of the CNN pincer osmium(II) derivatives **2–6**.

Complex **3**[8] is easily obtained in high yield upon treatment of $[OsCl_2(PPh_3)_3]$ with $Ph_2P(CH_2)_4PPh_2$ (dppb) and then with **1a** in the presence of NEt_3 (Scheme 1). The NCH_2 group gives a ^{13}C NMR signal at $\delta = 54.8$ ppm ($^3J_{C,P} = 2.6$ Hz), whereas the orthometalated carbon appears at $\delta = 161.5$ ppm ($^2J_{C,P} = 9.0$ and 3.9 Hz). The chiral pincer complex **4** was prepared in a similar manner to **3** but with dppb in combination with **1b** (85% yield), whereas **5** and **6** (55 and 47% yield, respectively) were obtained from (*S*,*R*)-Josiphos with **1a** and **1c**, respectively (Scheme 1).[8] ^{31}P NMR spectroscopic control experiments revealed the formation of different isomers in the reaction mixtures; the predominant stereoisomer was isolated from the reaction mixtures.

The osmium derivatives **2–6** were found to be highly active catalysts for the TH of different ketones **7** (0.1 M) in basic 2-propanol (Scheme 2). Thus, fast reduction of acetophenone (**7a**) into 1-phenylethanol is achieved in 10 min in refluxing 2-propanol (TOF = $1.8\times10^5\ h^{-1}$ at 50% conversion) in the presence of **2** (0.005 mol%) and NaO*i*Pr (2 mol%), while the reaction with **3** goes to completion in 5 min (TOF = $1.3\times10^6\ h^{-1}$; Table 1).[8] Surprisingly, this rate is slightly higher than that of the analogous compound [RuCl(CNN)(dppb)] (TOF = $1.1\times10^6\ h^{-1}$),[6c] which is one of the most active TH catalysts,[9] and, in contrast to the ruthenium-based catalysts, **3** also displays high activity with only one equivalent of NaO*i*Pr (TOF = $1.0\times10^6\ h^{-1}$).

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[*] Prof. W. Baratta, Dr. M. Ballico, Dr. K. Siega, Prof. P. Rigo
Dipartimento di Scienze e Tecnologie Chimiche
Università di Udine, Via Cotonificio 108, 33100 Udine (Italy)
Fax: (+39) 0432-558-803
E-mail: inorg@uniud.it
Dr. G. Chelucci
Dipartimento di Chimica, Università di Sassari
Via Vienna 2, 07100 Sassari (Italy)

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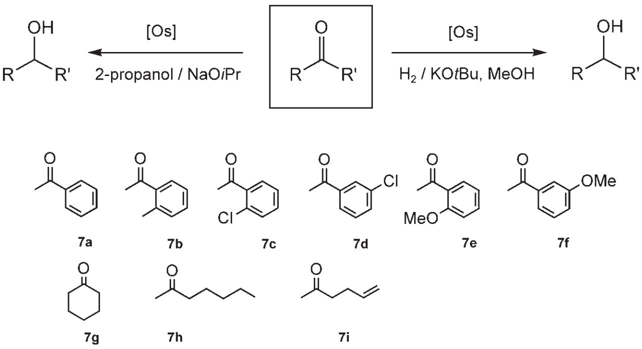


Scheme 2. TH and HY of ketones catalyzed by osmium(II) CNN pincer complexes (0.005–0.001 mol%).

Table 1: Catalytic TH of ketones (0.1 M) in the presence of **2**–**6** (0.005 mol% Os) and NaO*i*Pr (2 mol%) in 2-propanol.

Complex	Ketone	*T* [°C]	Conv. [%][a]	*t* [min]	TOF [h^{-1}][b]	*ee* [%][a]
2	**7a**	82	96	10	1.8×10^5	
3	**7a**	82	98	5	1.3×10^6	
3[c]	**7a**	82	97	60	4.3×10^5	
3	**7c**	82	99	5	9.0×10^5	
3	**7g**	82	95	10	6.0×10^5	
3	**7i**	82	96	10	4.0×10^5	
4	**7a**	60	94	120	1.2×10^5	74 *S*
5	**7a**	60	95	30	1.7×10^5	83 *S*
6	**7a**	60	97	30	1.7×10^5	93 *S*
6	**7b**	60	92	60	4.0×10^4	91 *S*
6	**7c**	60	96	30	1.3×10^5	90 *S*
6	**7e**	60	95	30	1.9×10^5	97 *S*
6	**7f**	60	94	10	2.0×10^5	97 *S*
6[d]	**7f**	70	94	120	4.0×10^5	97 *S*

[a] The conversion and *ee* values were determined by GC analysis. [b] Turnover frequency (moles of ketone converted per mol of catalyst per hour) at 50% conversion. [c] 0.001 mol% Os; [d] 0.002 mol% Os.

Complex **3** is highly active at even lower loadings (0.001 mol%) and affords complete conversion of **7a** in 1 h (TOF = 4.3×10^5 h^{-1}), whereas higher substrate/Os ratios lead to a turnover number (TON) of 1.4×10^5. It is noteworthy that [RuCl(CNN)(dppb)][6c] and $[IrH_3(iPr_2PC_2H_4)_2NH]$[10] are the only other systems which allow the TH of ketones at such low catalyst loadings.

Compound **3** is an efficient catalyst for the reduction of different types of ketones. Thus, **7c**, **7g**, and **7i** are rapidly and selectively converted into the corresponding alcohols (TOF of up to 9.0×10^5 h^{-1}). The asymmetric TH of methyl aryl ketones also proved possible with the chiral derivatives **4**–**6** (0.005 mol%) at 60 °C. Thus, **7a** is easily reduced to (*S*)-1-phenylethanol (TOF of up to 1.7×10^5 h^{-1}) with 74–93% *ee*, with the higher value being obtained for **6** (Table 1). The TH of **7b**, **7c**, **7e**, and **7f** in the presence of **6** leads to the corresponding (*S*)-alcohols with 91, 90, 97, and 97% *ee*, respectively (TOF of up to 2.0×10^5 h^{-1}). Importantly, ketone **7f** can also be reduced to (*S*)-1-(3-methoxyphenyl)ethanol (97% *ee* and 94% conversion) in 2 h at 70 °C with a very low loading of **6** (0.002 mol%; TOF = 4.0×10^5 h^{-1}). Chiral alcohols can therefore be prepared using these new pincer osmium complexes as catalyst with much lower loadings than usually needed for the majority of asymmetric TH catalysts (1–0.1 mol%) due to the easy deactivation of the latter.

Interestingly, these pincer osmium complexes are also active for the HY of ketones (0.5 M) in methanol with KO*t*Bu (0.05 mol%) under 5 atm of H_2 pressure at 60 °C (Scheme 2). Ketones **7a**, **7f**, **7g**, and **7h** are quantitatively converted into the corresponding alcohols within 1 h in the presence of 0.005 mol% of **3** (TOF of up to 3.3×10^4 h^{-1}; Table 2).[8]

Table 2: Catalytic HY of ketones (0.5 M) in the presence of **3**, **5**, or **6** (0.005 mol% Os) and KO*t*Bu (0.05 mol%) in methanol under 5 atm of H_2 pressure at 60 °C.

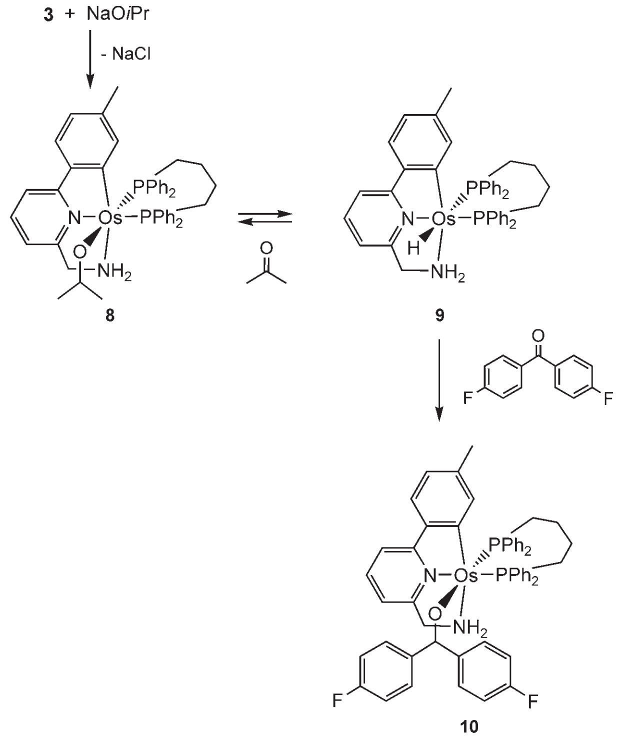
Complex	Ketone	Conv. [%][a]	*t* [h]	TOF [h^{-1}][b]	*ee* [%][a]
3	**7a**	> 99	1	2.5×10^4	
3[c]	**7a**	97	5	2.4×10^4	
3	**7f**	99	1	2.6×10^4	
3	**7g**	99	0.5	3.3×10^4	
3	**7h**	> 99	1	2.9×10^4	
5	**7a**	98	0.5	5.2×10^4	80 *S*
6	**7a**	99	2	1.2×10^4	86 *S*
6	**7e**	> 99	2	2.2×10^4	93 *S*
6	**7f**	> 99	2	2.0×10^4	98 *S*
6	**7d**	> 99	1	2.8×10^4	98 *S*
6[d]	**7d**	98	2	3.0×10^4	98 *S*

[a] The conversion and *ee* values were determined by GC analysis. [b] Turnover frequency (moles of ketone converted per mol of catalyst per hour) at 50% conversion. [c] 0.001 mol% Os; [d] 0.002 mol% Os, *T* = 70 °C.

It is worth noting that the reduction of **7a** is also possible at a lower loading of **3** (0.001 mol%, 5 h), thereby indicating that pincer osmium complexes also display a high productivity in HY. Complex **3** is also active in the HY of **7a** using only one equivalent of base (TOF = 2.4×10^4 and 1.8×10^4 h^{-1} with KO*t*Bu and NaO*i*Pr, respectively), although the rate of this reaction decreases at higher base/**3** ratios (> 20). Interestingly, the asymmetric HY of methyl aryl ketones has been achieved with the chiral osmium complexes **5** and **6** (0.005 mol%). Thus, hydrogenation of **7a** gives (*S*)-1-phenylethanol in 30 min and 2 h with 80 and 86% *ee*, respectively (Table 2). Similarly, ketones **7e**, **7f**, and **7d** are reduced to the corresponding (*S*)-alcohols with 93, 98 and 98% *ee*, respectively, within 2 h (TOF of up to 2.8×10^4 h^{-1}). Ketone **7d** is also quantitatively converted into (*S*)-1-(2-chlorophenyl)-ethanol (98% *ee*) in 2 h at 70 °C in the presence of a lower amount of **6** (0.002 mol%).

Chemoselective C=O hydrogenation of the aliphatic ketone **7i** is possible with **6**, but with only low enantioselectivity (10% *ee*), as is the reduction of **7h** (27% *ee*). Since reduction does not occur in the absence of H_2 (conversion < 1%), the reaction in methanol has to be regarded as a neat HY. To the best of our knowledge, this is the first example of an osmium complex that catalyzes the enantioselective HY of ketones.

As regards the species involved in TH and HY, it is reasonable to assume that complex **3** forms the corresponding osmium hydride complex in basic alcohol.[3a,11] Thus, treatment of **3** with one equivalent of NaO*i*Pr in 2-propanol/C_6D_6 (1:1 v/v) at room temperature affords a red solution containing a mixture of the osmium alkoxide **8**[8] stabilized by the alcohol and hydride **9** in a 4:1 molar ratio (Scheme 3). The ^{31}P NMR spectrum of **8** in 2-propanol shows two doublets at $\delta = 3.8$ and -0.3 ppm ($^2J_{P,P} = 9.7$ Hz). This species is in rapid equilibrium[12] with the hydride **9**, as inferred from variable-temperature ^{31}P NMR measurements.[13]



Scheme 3. Formation of osmium(II) alkoxide and hydride complexes.

Hydride **9** was isolated in 88% yield upon evaporation of the solvent from a 2-propanol/toluene solution of the **8/9** mixture by elimination of acetone.[8] The ^{1}H NMR signal for the Os-bound hydride appears as a doublet of doublets at $\delta = -5.32$ ppm ($^2J_{H,P} = 73.0$ and 23.7 Hz), which is consistent with the presence of *trans* and *cis* phosphorus atoms. The mixture **8/9** reacts with ketones, and alkoxide **10** was obtained in 74% yield upon treatment of this mixture with $(4\text{-}C_6H_4F)_2CO$ (Scheme 3).[8] The broad signal at $\delta = 5.08$ ppm in the ^{1}H NMR spectrum of this compound can be assigned to one NH proton and is consistent with an intramolecular NH···O hydrogen-bonding interaction. The singlets at $\delta = -119.3$ and -119.8 ppm in the ^{19}F NMR spectrum are for the two nonequivalent C_6H_4F groups and disappear upon addition of 4,4′-difluorobenzhydrol, which leads to a signal close to that of the free alcohol. The ^{31}P NMR spectrum of **10** in the presence of this alcohol shows two doublets at $\delta = 2.5$ and 0.6 ppm ($^2J_{P,P} = 9.0$ Hz) in addition to those of **10**, which is consistent with the formation of the alcohol adduct **10**·(ROH). It should be pointed out that the synthesis of **10** is accomplished without isolation of the hydride and by exploiting the higher redox potential of the diaryl ketone compared to Me_2CO.[14]

Since our investigations show that chloride **3** forms an equilibrium mixture of hydride and alkoxide complexes in basic alcohol, it is probable that these species are involved in both TH[7b,15] and HY. Thus, $[OsH(CNN)P_2]$ is likely to be a key species in both catalytic reactions and leads to the alkoxide $[Os(OR)(CNN)P_2]$ upon reaction with the ketone substrate. Protonation of $[Os(OR)(CNN)P_2]$ with 2-propanol or methanol gives $[Os(OR')(CNN)P_2]$ (R′ = *i*Pr, Me) and the alcohol product with much the same *ee* value in both TH and HY. However, while in TH the Os-O*i*Pr species equilibrates to acetone and $[OsH(CNN)P_2]$, thereby closing the catalytic cycle, the osmium hydride is regenerated in HY by heterolytic H_2 splitting promoted by the Os-OMe species. The high catalytic activity and productivity of this robust osmium system can be ascribed to the formation of Os-X (X = H, OR) species with X *trans* to a phosphorus atom and *cis* to the CNN ligand. As the Os-NH_2 linkage is involved in hydrogen-bond interactions with the ketone and alcohol, the flat pyridine system may favor the access of the substrate.

In conclusion, we have described the isolation of the first CNN pincer osmium complexes $[OsX(CNN)P_2]$ to display high catalytic activity and productivity in the reduction of ketones by either TH or HY (TOF and TON up to 10^6 h^{-1} and 10^5, respectively). A high enantioselectivity (up to 98% *ee*) is possible in both reactions with a remarkably low catalyst loading (0.005–0.002 mol%). To the best of our knowledge, this is the first example of an osmium complex that catalyzes the asymmetric HY of ketones. Evidence for an Os-OR vs. Os-H equilibrium suggests that both these species are involved in the catalytic pathways. Mechanistic studies as well as the preparation of new CNN pincer osmium catalysts are currently underway.

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