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PAPER

Pincer Ru and Os complexes as efficient catalysts for racemization and deuteration of alcohols

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The pincer complexes [MX(CNN)(PP)] (M = Ru, Os; X = Cl, OTf; HCNN = 1-(6-arylpyridin-2-yl)methanamine; PP = diphosphine) have proven to efficiently catalyze both racemization and deuteration of alcohols in the presence of a base. Chiral alcohols have been racemized at 30–50 °C using 1 mol% of Ru or Os pincer complexes and 5 mol% of KO*t*Bu in 2-propanol. Primary and secondary alcohols are efficiently deuterated at the α position, with respect to the OH group, using 2-propanol-d_8 as solvent with Ru or Os pincer complexes and KO*t*Bu at 30–50 °C. For secondary alcohols incorporation of deuterium at the β position has also been observed. In 2-propanol-d_8 the pincer complexes catalyze the simultaneous deuteration and racemization of (*S*)-1-phenylethanol, the two processes being strictly correlated. For both reactions much the same activity has been observed with the Ru and Os complexes. The pincer complexes display a superior activity with respect to the related compounds [MCl_2(NN)(PP)] (NN = bidentate amine or pyridine ligand). The synthesis of the new complexes [MCl(CNN)(PP)] (M = Ru, **2**, **4** and Os, **6**, **7**; PP = dppb, dppf) and [Ru(OTf)(CNN)(dppb)] (**3**) is also reported.

Introduction

Activation of the C–H bond vicinal to the hydroxyl group is a fundamental step for broadening the reactivity of alcohols. In this context, the racemization of alcohols mediated by transition metal complexes is an important transformation that in association with the kinetic resolution can allow the preparation of optically active alcohols.[1] Efficient dynamic kinetic resolution (DKR) has been achieved through the combination of a lipase with a number of ruthenium complexes,[2] based on the pioneering work of Bäckvall on the Shvo catalyst.[3] Conversely, the C–H bond activation is a crucial process in the catalytic H/D exchange at the carbon centers of alcohols for obtaining deuterium-labeled compounds for pharmaceutical and analytical chemistry.[4] Several systems, including [$RuCl_2(PPh_3)_3$] and supported Ru and Pd have been found as efficient catalysts for the deuteration of alcohols using D_2O.[5] In addition, the C–H bond activation at the α position represents a key step for increasing the alcohol reactivity for C–C and C–N coupling reactions which occur through borrowing hydrogen.[6] Most of these catalytic reactions entail the reversible alcohol dehydrogenation with formation of the more reactive carbonyl compound (aldehyde, ketone). Among the different metals used for these processes, ruthenium has widely been investigated and the search for new catalysts able to activate alcohols under mild conditions remains a challenge. On the basis of the microscopic reversibility, it is expected that highly active catalysts for transfer hydrogenation (TH)[7] of carbonyl compounds can also induce the activation of alcohols. Incidentally, the pincer complexes [MCl(CNN)(PP)][8] (M = Ru, Os; HCNN = 1-(6-arylpyridin-2-yl)methanamine; PP = diphosphine), displaying the NH_2 function,[9] are among the most efficient catalysts for the TH of aldehydes and ketones. These systems are also active in the hydrogenation[10] of carbonyl compounds[8b,d] and in the dehydrogenation of alcohols.[11] Kinetic and NMR studies show that under catalytic conditions, the chloride [RuCl(CNN)(dppb)] (**1**) (dppb = 1,4-bis(diphenylphosphino)butane) reacts with NaO*i*Pr in *i*PrOH, affording the Ru isopropoxide which rapidly equilibrates (<1 s at RT) with the corresponding Ru hydride and acetone (Scheme 1).[12]

In this rare example of directly observable oxidation-reduction pathway,[13] both the NH_2 function and the solvent (2-propanol) play an active role in facilitating the activation of the α C–H bond of the substrate within a hydrogen bonding network.[12] The same behavior has been observed for the analogous osmium complexes.[8d] This reversible C–H bond cleavage mediated by pincer complexes opens the way for a broader reactivity of alcohols *via* carbonyl intermediates. Arends *et al.* have demonstrated that **1** is active in the racemization of 1-phenylethanol in toluene at 70 °C.[14] More recently, fast racemization of alcohols has been reported by Feringa *et al.* with half sandwich NH ruthenacycle catalysts[15] and by Nolan and Bosson using Ru complexes with N-heterocyclic carbenes.[16]

We describe here that the pincer Ru and Os complexes [MX(CNN)(PP)] (X = Cl, OTf) **1–8** in the presence of the base KO*t*Bu in 2-propanol display high catalytic activity in the racemization of secondary alcohols at 30–50 °C (Fig. 1).

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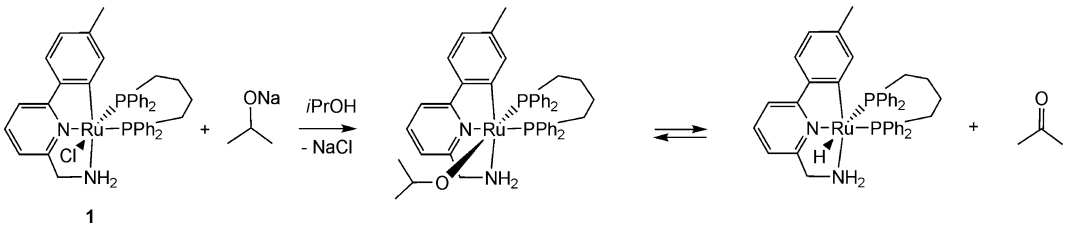


Scheme 1 Formation of a RuO*i*Pr complex and equilibrium between RuO*i*Pr *vs.* RuH/acetone.

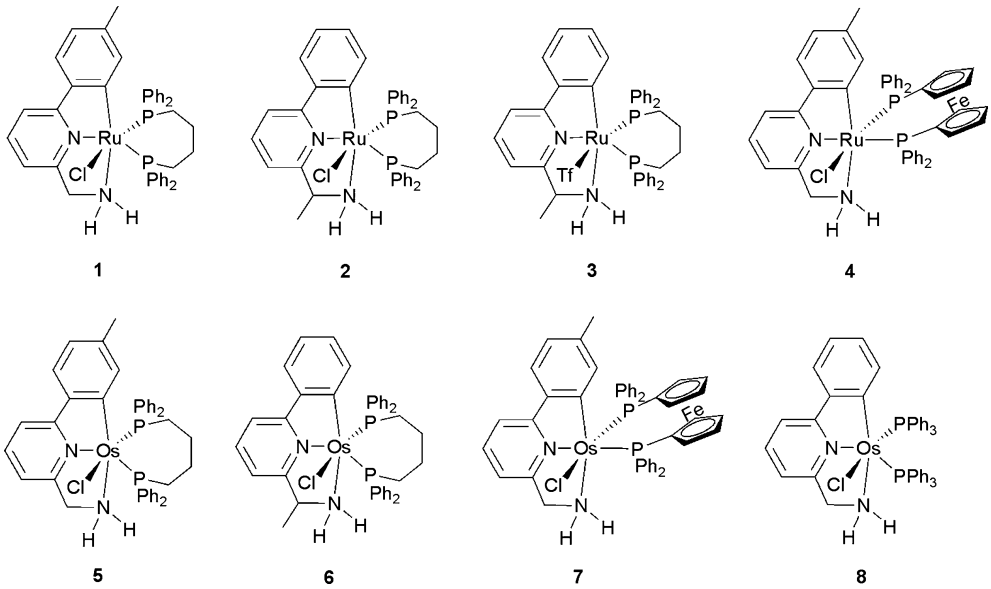


Fig. 1 Ru and Os pincer complexes [MX(CNN)(PP)].

These catalysts are also highly efficient in the deuteration of primary and secondary alcohols in 2-propanol-d_8 and their activity has been compared with that of the related hydrogenation and TH systems $[MCl_2(NN)(PP)]$ (**9–14**) (NN = bidentate amine or pyridine ligand) (Fig. 2).

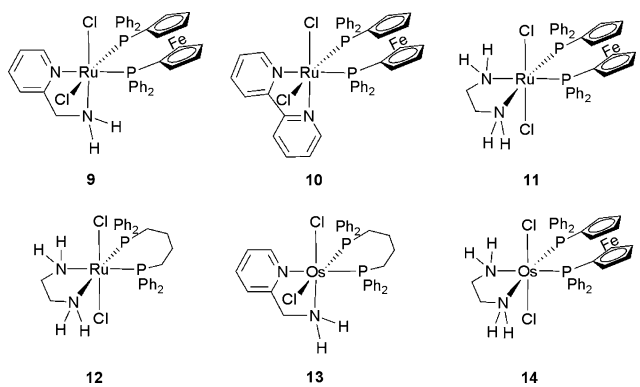


Fig. 2 Ru and Os complexes $[MCl_2(NN)(PP)]$ (NN = bidentate amine or pyridine ligand).

To the best of our knowledge, no examples of Os catalysts for racemization and deuteration of alcohols have previously been described. The isolation of the new pincer complexes of ruthenium (**2–4**) and osmium (**6**, **7**), some of them containing 1,1′-bis(diphenylphosphino)ferrocene (dppf), is also reported.

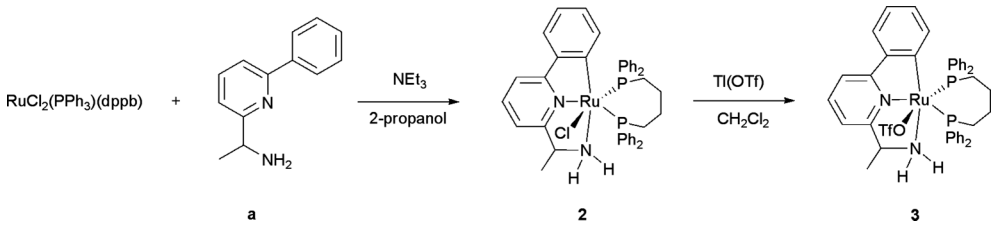
Results and discussion

Synthesis of the pincer complexes 2, 3, 4, 6 and 7

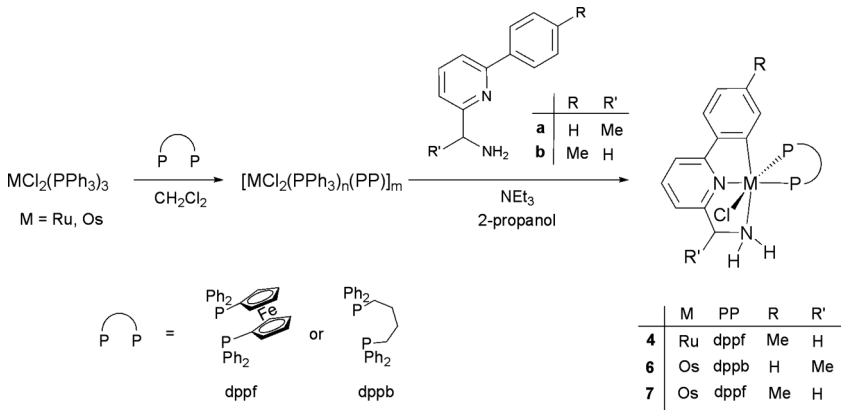
The orthometalated ruthenium(II) complex **2** was easily obtained in high yield by reaction of the precursor $[RuCl_2(PPh_3)(dppb)]$ with an equimolar amount of *rac*-1-(6-phenylpyridin-2-yl)ethanamine (**a**) in 2-propanol at reflux in the presence of NEt_3 in excess, according to the procedure reported for **1** (Scheme 2).[17]

On account of the presence of two stereogenic centers on the Ru and C–Me, four stereoisomers are expected. The $^{31}P\{^1H\}$ NMR spectrum of **2** shows two doublets at $\delta = 57.4$ and 42.1 ppm with $^2J_{PP} = 38.7$ Hz, whereas the ^1H NMR spectrum displays a doublet at $\delta = 1.44$ ppm for the methyl group, in agreement with the formation of **2** as a one pair of enantiomers. This agrees with the previous studies on the analogous complex bearing a *tert*-butyl group adjacent to NH_2, suggesting that in the racemate **2** the methyl group points towards the chloride.[17]

Treatment of **2** with one equivalent of thallium triflate in CH_2Cl_2 at room temperature (4 h), afforded the derivative **3** (Scheme 2).[18] The $^{31}P\{^1H\}$ NMR spectrum shows two broad signals at $\delta = 66.0$ and 42.1 ppm for a single species, while the ^{19}F NMR shows a singlet at $\delta = -77.6$ ppm, slightly shifted downfield with respect to the free triflate anion ($\delta \sim -80.0$),[19] suggesting a weak coordination of the oxygen donor ligand.[20] By difference to **2**, complex **3** displays a relatively high solubility in different organic solvents, such as toluene and *i*PrOH.



Scheme 2 Syntheses of the Ru complexes **2** and **3**.



Scheme 3 Syntheses of the Ru complex **4** and the Os complexes **6** and **7**.

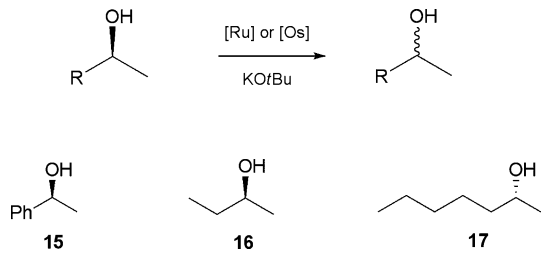
The pincer derivative **4**, containing a flexible ferrocene diphosphine,[21] has been prepared by reaction of $[RuCl_2(PPh_3)_n$-$(dppf)]_m$ with 1-[6-(4′-methylphenyl)pyridin-2-yl]methanamine (**b**) in the presence of NEt_3 in 2-propanol at reflux temperature. The intermediate $[RuCl_2(PPh_3)_n(dppf)]_m$ was obtained from $[RuCl_2(PPh_3)_3]$ with dppf in dichloromethane at RT (2 h) (Scheme 3).[22]

The $^{31}P\{^1H\}$ NMR spectrum of **4** shows two doublets at δ = 62.4 and 45.1 ppm with $^2J_{PP}$ = 36.0 Hz. The osmium pincer **6**, analogous to the ruthenium **2**, has been prepared by treatment of $[OsCl_2(PPh_3)_3]$ with dppb in CH_2Cl_2 at RT (3 h) and reaction with the ligand **a** and triethylamine (10 equiv.) in 2-propanol at reflux temperature (3 h) (Scheme 3).[8d] Similarly, the ferrocenyl derivative **7** has been obtained from $[OsCl_2(PPh_3)_3]$, dppf and the pincer **b**. The $^{31}P\{^1H\}$ NMR spectrum of **7** shows two doublets at δ = 4.6 and 0.7 ppm with $^2J_{PP}$ = 20.2 Hz. By contrast **6** shows only a singlet at δ = 0.28 ppm, indicating that the two P atoms have nearly the same chemical shift. The ^1H and $^{13}C\{^1H\}$ NMR spectra of **6** and **7** are similar to those of the related ruthenium complexes **2** and **4**, respectively, in agreement with the formation of six-coordinate amino complexes. It is to point out that the five coordinate amido species, which could form from the amino complexes by elimination of HCl, have not been observed.

Racemization

The pincer complexes **1**–**8** (Fig. 1) in the presence of KO*t*Bu have proven to efficiently catalyze the racemization of the optically active secondary alcohols (Scheme 4).

The substrate (*S*)-1-phenylethanol **15** (about 0.3 M), which was used as a model substrate, is promptly racemized by complex **1** (1 mol%) in 2-propanol with KO*t*Bu (5 mol%) at 30 °C in 2 h (entry 1 of Table 1).



Scheme 4 Racemization of chiral alcohols catalyzed by Ru and Os pincer complexes.

The same result (0% *ee*) is obtained using a 2-propanol/toluene mixture (1/1 in volume) (entry 2). Under these catalytic conditions, no racemization occurs with **1** without base, indicating that KO*t*Bu is crucial for the generation of the catalytically active ruthenium hydride species (entry 3). Under these experimental conditions, no formation of acetophenone, *i.e.*, the product of dehydrogenation, was observed *via* GC analysis. Complex **2**, bearing a methyl group adjacent to the NH_2 function, catalyzes the complete racemization in 1 h at 30 °C, indicating that the methyl substituent does not inhibit the catalysis (entry 4). The highly soluble triflate **3** is apparently less efficient leading to 18% *ee* in 2 h (entry 5). The complex **4**, containing the ferrocenyl diphosphine, displays a lower activity at 30 °C (26% *ee* in 2 h), whereas at 50 °C complete racemization is attained in 1 h (entries 6 and 7). Interestingly, the osmium pincer **5** is found extremely active, leading to complete racemization in 1 h at 30 °C and within 40 min at 50 °C (entries 8 and 9). The comparison of these data with those of the corresponding ruthenium complex, indicates that osmium is more active with respect to ruthenium for which the reaction is complete in 2 h.[23] With NaO*i*Pr, **5** displays much the same rate as with KO*t*Bu (entry 10), while no reaction occurs in the

Table 1 Racemization of **15** catalyzed by Ru and Os complexes (1.0 mol%) with KO*t*Bu (5.0 mol%) in 2-propanol

Entry	Catalyst	*T*/°C	Time/h	*ee* (%)
1	**1**	30	2	0
2[a]	**1**	30	2	0
3[b]	**1**	30	2	99
4	**2**	30	1	0
5	**3**	30	2	18
6	**4**	30	2	26
7	**4**	50	1	0
8	**5**	30	1	0
9	**5**	50	40 min	0
10[c]	**5**	30	1	0
11[d]	**5**	30	2	99
12	**6**	30	2	0
13	**7**	30	2	40
			4	0
14	**7**	50	2	0
15	**9**	30	2	96
16	**9**	90	45 min	0
18	**10**	30	2	99
19	**10**	90	2	99
20	**11**	30	2	99
21	**12**	90	4	10
17	**13**	30	2	38
22	**14**	30	2	99

[a] The reaction was carried out in 2-propanol/toluene (1/1 in volume). [b] Without base. [c] Base: NaO*i*Pr (5.0 mol%). [d] Base: DBU (5.0 mol%).

presence of the DBU base (entry 11). For the methyl substituted **6**, complete racemization is attained in 2 h (entry 12). Similarly to the ruthenium **4**, the ferrocenyl osmium complex **7** shows a lower rate, affording at 30 °C complete racemization in 4h, whereas at 50 °C the reaction occurs in 2 h (entries 13 and 14). The higher temperature requested for the dppf Ru and Os derivatives may be related to the lower basicity of dppf, with respect to dppb, which may hinder the chloride dissociation and the formation of the catalytically active M–H species. The comparison of the catalytic activity of the Noyori type complexes $[MCl_2(NN)(PP)]$, bearing bidentate amine or pyridine ligands, shows that these systems are less active with respect to the pincer complexes. The *cis* 2-aminomethylpyridine Ru complex **9**, which is related to **4**, is almost not active at 30 °C and affords racemization in 45 min at 90 °C (entries 15, 16). It is worth noting that the *cis* dipyridine compound **10** displays no catalytic activity even at 90 °C (entries 18, 19). Regarding the *trans* diamine complexes, the ferrocenyl **11** is not active at 30 °C (entry 20), while **12** bearing dppb leads to 10% *ee* after 4 h at 90 °C (entry 21). For osmium, the ampy derivative **13**, which is related to the pincer **5**, affords 38% *ee* at 30 °C (2 h), while the diamine **14** is not active under these conditions (entry 22).

These results show that pincer ruthenium and osmium complexes display much the same activity in the racemization reaction. In addition, these compounds are more active with respect to the derivatives $[MCl_2(NN)(PP)]$, where the order of activity is ampy > diamine > dipyridine.

The racemization of **15** was also carried out in non protic solvents, such as toluene in the presence of a weak base. This point is of particular importance for applications in DKR in which the enzymatic reaction is generally not compatible with strong bases. By using the labile triflate **3** (1 mol%) and NEt_3, in place of KO*t*Bu, no racemization was observed at 50 °C in 2 h (entry 1), whereas

Table 2 Racemization of **15** catalyzed by Ru and Os catalysts (1.0 mol%) in the presence of base (5 mol%) in toluene

Entry	Catalyst	Base	*T*/°C	Time/h	*ee* (%)	Ketone (%)
1	**3**	NEt_3	50	2	99	0
2	**3**	DBU	50	2	78	16
				5	2	33
3	**3**	DBU[a]	70	6	2	18
4	**4**	DBU	70	4	99	0
5	**5**	KO*t*Bu	30	2	10	0
6	**5**	DBU	70	4	99	0
7	**5**	K_2CO_3	30	2	99	0
8	**7**	DBU	70	24	86	8
9	**7**	DBU[a]	90	6	0	8
10	**9**	DBU	70	6	99	0
11	**12**	DBU	70	6	99	0

[a] Base 10 mol%.

with DBU (5 mol%) the *ee* were 78 and 2% after 2 and 5 h, respectively (entry 2) (Table 2).

It is worth noting that using toluene instead of *i*PrOH leads to concomitant formation of acetophenone (33% in 5 h) *via* a dehydrogenation reaction. By increasing the amount of base (DBU 10 mol%) racemization occurs within 6 h at 70 °C and with lower formation of acetophenone (18%, entry 3), indicating that both the base and the solvent affect the selectivity of the racemization reaction. The ferrocenyl complex **4** with DBU is not active even at 70 °C (entry 4). The osmium **5** with KO*t*Bu gives 10% *ee* in 2 h at 30 °C without dehydrogenation (entry 5), while no reaction occurs with DBU at 70 °C (entry 6) or K_2CO_3 at 30 °C (4 h, entry 7). The ferrocenyl derivative **7** in the presence of DBU (5 mol%) leads to 86% *ee* at 70 °C in 24 h (entry 8). By increasing the amount of base (10 mol%), complete racemization is achieved at 90 °C after 6 h (entry 9). Finally the $[MCl_2(NN)(PP)]$ complexes **9** and **12** in the presence of DBU were found not active at 70 °C (entries 10, 11). The comparison of the activity of the pincer complexes in toluene *vs.* 2-propanol shows that high racemization rate is achieved in the protic media and in the presence of a strong base. While in 2-propanol (hydrogen donor) quantitative racemization of 1-phenylethanol is achieved without formation of side products, in toluene catalytic dehydrogenation to acetophenone is also observed, depending on the temperature and base used.

Chiral aliphatic alcohols have also been racemized by the pincer complexes in 2-propanol. With the ruthenium **1** (1 mol%) and KO*t*Bu (5 mol%), (*S*)-2-butanol **16** is completely converted into the racemate in 2 h at 50 °C (entry 1) (Table 3).

A similar activity has been observed with **2** (entry 2), whereas the ferrocenyl **4** affords 4% *ee* in 2 h (entry 3). The osmium derivatives **5** and **6** give the racemization in 4 and 2 h (entries 4, 5), respectively, whereas **7** shows poor catalytic activity (64% *ee* in 2 h) (entry 6). Finally, the substrate (*R*)-heptanol **17** is racemized at 50 °C with the ruthenium complexes **1**, **2** and **4** in 2 h (entries 7–9). Also the osmium complexes **5** and **6** lead to complete racemization in 2 h (entries 10 and 11), whereas **7** shows moderate activity (48% *ee*, 2 h).

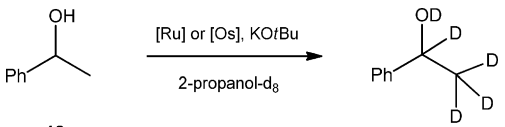
Deuteration

The pincer Ru and Os complexes in the presence of KO*t*Bu have also been found to be efficient catalysts for the deuteration of

Table 3 Racemization of **16** and **17** catalyzed by pincer Ru and Os complexes (1.0 mol%) with KO*t*Bu (5.0 mol%) in 2-propanol at 50 °C

Entry	Substrate	Catalyst	Time/h	*ee* (%)
1	**16**	**1**	2	0
2	**16**	**2**	2	0
3	**16**	**4**	2	4
4	**16**	**5**	4	0
5	**16**	**6**	2	0
6	**16**	**7**	2	64
7	**17**	**1**	2	0
8	**17**	**2**	2	0
9	**17**	**4**	2	0
10	**17**	**5**	2	0
11	**17**	**6**	2	0
12	**17**	**7**	2	48

alcohols in 2-propanol-d_8. For secondary alcohols fast deuterium incorporation at the α and β positions to the hydroxyl group is easily achieved at 30–60 °C within a few hours using 1 mol% of catalyst. With complex **1**, *rac*-1-phenylethanol **18** undergoes H–D exchange at CH–O (96%) and CH_3 (80%) in 2 h at 30 °C, as established by NMR measurements (entry 1, Table 4).



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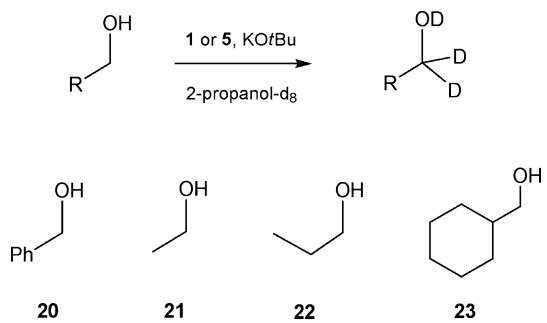
High deuterium incorporation into the substrate is accomplished using 2-propanol-d_8 in large excess (2-propanol-d_8/substrate = 40), which takes H in the α and β positions. As a matter of fact, nearly all quantitative hydrogen exchange at the α position of the substrate and 2-propanol-d_8 has been inferred from ^{1}H NMR measurements. In addition, in the basic protic media the substrate is present as ROD since the hydroxyl O–H/O–D exchange occurs instantaneously. Without base, insignificant deuteration at the α position (< 4%) is observed with no β incorporation, indicating that the H-D exchange is catalyzed by Ru. Using D_2O in place of 2-propanol-d_8 at 50 °C the deuteration is much slower and leads unexpectedly to a higher D content at the β position (94% in 24 h) with respect to the α position (54%) (entry 3). Similarly to **1**, complex **2** catalyzes the deuteration of **18** at 30 °C in 2-propanol-d_8, leading to 91 and 60% of D incorporation at the α and β positions, while **4** gives 87 and 77% (4 h), respectively (entries 4, 5). Also the osmium derivatives **5** and **7** have been found to be highly active in the catalytic H - D exchange at 30 °C, leading to 96 (2 h) and 92% (4 h) of α deuteration, while the values for the β incorporation are 90 and 84%, respectively (entries 6, 7), the activity of **5** being comparable with that of **1**. To show the synthetic potential of this reaction, 1-phenylethanol-d_5 (110 mg, purity >98%) has easily been prepared in 87% yield by reaction of **18** (1.0 mmol) with 2-propanol-d_8 (2 × 1.5 mL), using 0.5 mol% of **5** in the presence of KO*t*Bu (2.5 mol%) at 40 °C. Although D_2O is the cheapest source for obtaining deuterium-labeled compounds, the use of 2-propanol-d_8 in combination with pincer complexes is a straightforward procedure for the deuteration of alcohols. The comparison of the catalytic activity of the pincer complexes with the derivatives [MCl_2(NN)(PP)], shows that the latter are less active as for the racemization reaction. The ampy complex **13** gives 40 and 41% of α and β exchange at 30 °C (entry 8), whereas the diamine **12** is less active (entries 9 and 10). Conversely, at 60 °C **12** catalyzes the H–D exchange affording 93 (α) and 89% (β) of D content in 2 h (entry 10). With **1** at 30 °C, 2-heptanol **19** undergoes deuteration at the α position (50% in 24 h) with a lower rate with respect to **18** (entry 11). At 70 °C almost quantitative D incorporation has been attained for the α hydrogen (99%), as well as the CH_3 and CH_2 β hydrogens in 4 h, as established by ^{1}H and ^{13}C NMR experiments (entry 12).

Primary alcohols are efficiently deuterated at the α position using the pincer complexes. Benzyl alcohol **20** easily incorporates deuterium at 50 °C in 1 h (94%) with **1** (1 mol%) in 2-propanol-d_8 (entry 1, Table 5) (Scheme 5).



20 **21** **22** **23**

Scheme 5 Deuteration of primary alcohols catalyzed by complex **1**.

Table 4 Deuteration of secondary alcohols catalyzed by Ru and Os complexes (1 mol%) in the presence of KO*t*Bu (5 mol%) in 2-propanol-d_8

Entry	Substrate	Catalyst	*T*/°C	Time/h	D content in α (%)	D content in β (%)[a]
1	**18**	**1**	30	2	96	80
2	**18**	—	30	2	4	0
3[b]	**18**	**1**	50	24	54	94
4	**18**	**2**	30	2	91	60
5	**18**	**4**	30	4	87	77
6	**18**	**5**	30	2	96	90
7	**18**	**7**	30	4	92	84
8	**18**	**13**	30	2	40	41
9	**18**	**12**	30	2	11	0
10	**18**	**12**	60	2	93	89
11	**19**	**1**	30	24	50	40
12	**19**	**1**	70	4	99	96[c]

[a] For the methyl group. [b] The reaction was carried out in D_2O. [c] Complete methylene deuteration was inferred from ^{13}C NMR.

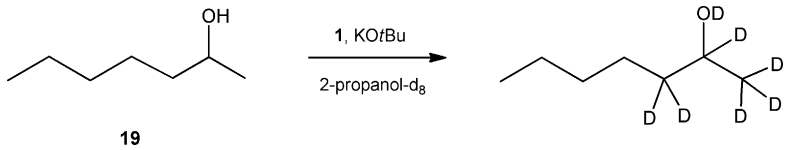


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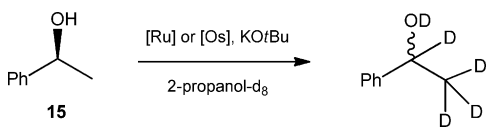
Table 5 Deuteration of primary alcohols catalyzed by **1** and **5** (1 mol%) with KO*t*Bu (5 mol%) in 2-propanol-d_8 at 50 °C

Entry	Substrate	Catalysxt	Time/h	D content in α (%)	D content in β (%)
1	**20**	**1**	1	94	/
			3	95	/
2	**21**	**1**	1	98	0
3[a]	**21**	**1**	24	0	0
4	**22**	**1**	1	94	0
			3	99	7
			5	99	14
5	**22**	**5**	0.5	90	0
			1	95	0
6	**23**	**1**	1	94	0
			2	95	0
			4	95	0

[a] The reaction was carried out in D_2O.

Interestingly, ethanol **21** is deuterated at the α position in 1 h (98%), with no significant incorporation of D at the β position (entry 2). No deuteration of **21** has been observed with **1** using D_2O, in place of 2-propanol-d_8, after 1 day (entry 3). Similarly to **21**, 1-propanol **22** undergoes incorporation of D at the α position, namely 94 and 99% after 1 and 3 h, respectively (entry 4). The ^{1}H NMR measurements carried out after 3 and 5 h show moderate deuteration at the β position (7 and 14%). High catalytic activity has also been observed with the osmium **5** which leads to 95% of α incorporation in **22** after 1 h. Finally, also cyclohexylmethanol **23** has been deuterated at the α position (95% 2 h), without D incorporation at the β position (entry 6).

When a chiral alcohol is dissolved in 2-propanol-d_8 the pincer complexes catalyze simultaneously the racemization and deuteration reactions. With complex **1** (1 mol%) at 30 °C and in the presence of KO*t*Bu (5 mol%), (*S*)-1-phenylethanol **15** undergoes racemization in 2 h (3% *ee**)[24] with D incorporation at the α and β positions of 95 and 70%, respectively.



15

After 4 h, complete racemization and higher deuteration in both positions (99 and 95%) has been observed (entry 1, Table 6).

By employment of the osmium complex **5** the reaction is faster leading to 0% *ee** and nearly quantitative D incorporation at the α and β positions in 1 h (entry 2). The osmium derivative **8** bearing PPh_3 is significantly less active compared to the analogous diphosphine complexes, affording 64% *ee** with 36 and 39% of deuterium content at the α and β positions after 1 h, whereas complete racemization and deuteration is attained after 24 h (entry 3). The data of Table 6 show that

$$ee^* + (\%)_{\alpha D} = 100$$

within the experimental errors. From the definition of *ee** and $(\%)_{\alpha D}$ [24] follows that

$$ee^* + (\%)_{\alpha D} = 100 \times (S_H + S_D - R_D)/(S_H + S_D + R_D) + 100 \times (S_D + R_D)/(S_H + S_D + R_D) = 100 \times (S_H + 2S_D)/(S_H + S_D + R_D)$$

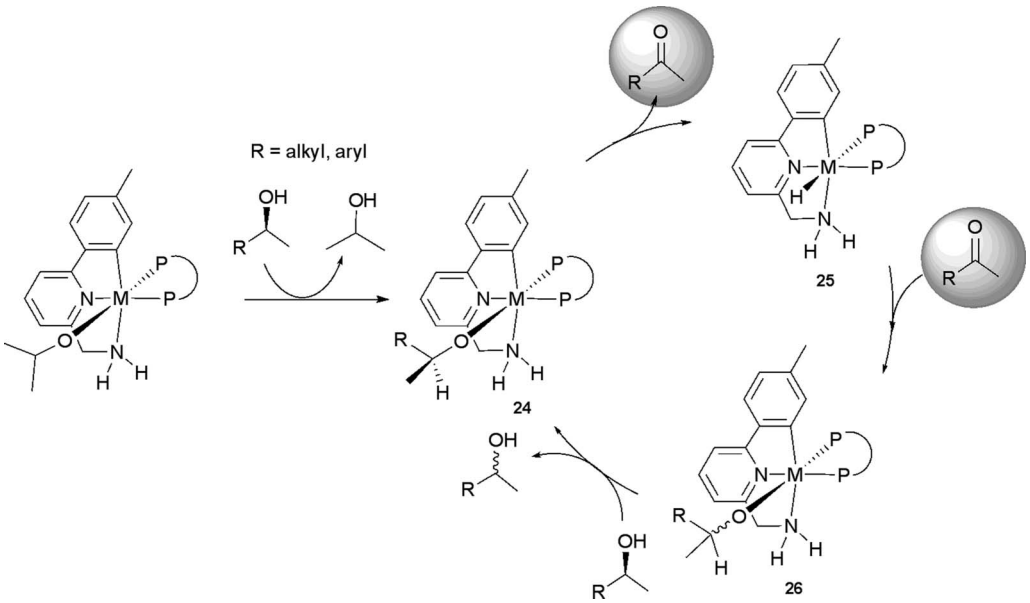
According to the first equation, this implies that $S_D = R_D$ and therefore the α deuteration occurs with racemization and not through a C–H/D exchange with retention of the configuration at the carbon atom, indicating that the two reactions are strictly correlated and occur simultaneously.

The results of this study on the racemization and deuteration of alcohols with the pincer Ru and Os complexes, are in agreement with a mechanism involving the reversible formation of ketone (aldehyde) through a hydrogen transfer reaction.[25] In the proposed catalytic cycle for the alcohol racemization, the isopropoxide

Table 6 Racemization and deuteration of **15** catalyzed by **1**, **5** and **8** (1 mol%) with KO*t*Bu (5 mol%) in 2-propanol-d_8 at 30 °C

Entry	Catalyst	Time/h	*ee** (%)[a]	D content in α (%)	D content in β (%)
1	**1**	2	3	95	70
		4	0	99	95
2	**5**	1	0	97	97
		2	0	99	98
3	**8**	1	64	36	39
		24	0	97	97

[a] $ee^* = 100 \times (S_H + S_D - R_D)/(S_H + S_D + R_D)$



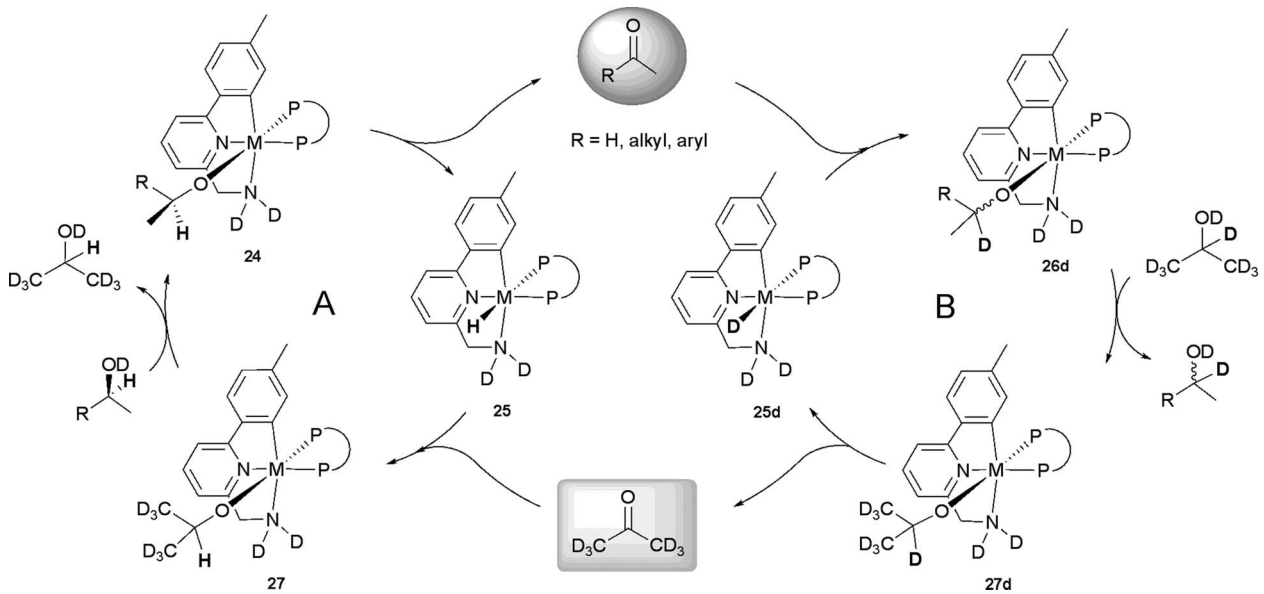
Scheme 6 Proposed catalytic cycle for the racemization of alcohols catalyzed by Ru and Os pincer complexes in 2-propanol.

[M(O*i*Pr)(CNN)(PP)], which is formed from [MX(CNN)(PP)] in basic 2-propanol, is protonated by the chiral substrate leading to the alkoxide [M(OC*HRMe)(CNN)(PP)] (**24**) (Scheme 6).

This species affords the hydride [MH(CNN)(PP)] (**25**) with extrusion of the ketone through a β hydrogen elimination reaction, assisted by the NH_2 function and the 2-propanol media.[12a] The non enantioselective reduction of the ketone affords [M(OCHRMe)(CNN)(PP)] (**26**) which is protonated by the chiral alcohol, affording the racemic alcohol and closing the cycle. This mechanism resembles that proposed by Bäckvall *et al.* for cyclopentadienyl Ru systems,[26] although at this stage it is not clear whether in protic media the formed ketone remains close to the Ru hydride or it is free, leading to reduction, but not at the same Ru–H center.

Conversely, if the reaction is performed in 2-propanol-d_8, primary and secondary (chiral) alcohols are converted to carbonyl compounds and reduced to the α deuterium-labeled (racemic) alcohols by a metal deuteride (Scheme 7).

The catalytic pathway may be envisioned as composed by two mirrored cycles, identical to that proposed for the alcohol racemization, namely cycle A involving M–H and cycle B for M–D species. In the basic media, the precursor [MX(CNN)(PP)] reacts with the alcohol substrate and 2-propanol-d_8 affording the alkoxides [M(OCHRMe)(CNN)(PP)] (**24**) and [M(O*i*Pr-d_7)(CNN)(PP)] (**27d**), respectively. According to the previous mechanism, **24** leads to the hydride [MH(CNN)(PP)] (**25**) with elimination of the carbonyl compound, whereas **27d** gives the deuteride [MD(CNN)(PP)] (**25d**) and acetone-d_6. The



Scheme 7 Proposed catalytic pathway for the deuteration of alcohols catalyzed by Ru and Os pincer complexes in 2-propanol-d_8.

subsequent "cross" reactions of the free carbonyl compound with **25d** and acetone-d_6 with **25** give the corresponding alkoxides [M(OCDRMe)(CNN)(PP)] (**26d**) and [M(O*i*Pr-d_6)(CNN)(PP)] (**27**). Finally, protonation of these species leads to the α deuterated alcohol substrate and the 2-propanol-d_7, closing the cycles. In basic 2-propanol-d_8 the NH_2 function of the catalyst is likely converted into the ND_2 moiety, due to the facile H/D exchange.[17] Although in 2-propanol-d_8 an alternative pathway for the Ru–D formation, involving a Ru–H/D–O exchange, cannot be ruled out, this process appears less likely, since use of D_2O retards drastically the deuteration. It is worth noting that these data show that the α hydrogens are exchanged more rapidly compared to the β ones. While primary alcohols give moderate or negligible incorporation at the β position, secondary alcohols give fast deuteration at the CH_3, whereas the β CH_2 moiety of the alkyl chain is slowly deuterated. No exchange has been observed for γ or aromatic hydrogen atoms and for the CH_3 of the *t*BuOH, formed from KO*t*Bu, as inferred from ^{1}H and ^{13}C NMR measurements. This agrees with the oxido-reductive cycle in which the β hydrogens of the alcohols undergo in the basic media deuterium exchange through the formation of the corresponding carbonyl compound, namely at the CH close to the C═O group *via* enolates. The difference of the behavior of primary *vs.* secondary alcohols are in agreement with the literature data,[4a] and may be ascribed to the higher redox potential of the aldehydes compared to the ketones,[27] affording a lower amount of free aldehyde *vs.* ketone in solution.

Conclusion

In summary, we have found that the pincer complexes [MCl(CNN)(PP)] (M = Ru, Os; PP = diphosphine) in basic 2-propanol are efficient catalysts for the racemization of secondary alcohols in basic 2-propanol. These systems also efficiently catalyze the deuteration of primary and secondary alcohols in 2-propanol-d_8. In addition to the α incorporation of deuterium with respect to the OH group, the secondary alcohols undergo deuteration at the β position. Much the same activity has been observed for the ruthenium and osmium pincer complexes, which are superior with respect to the complexes [MCl_2(NN)(PP)] (NN = bidentate amine or pyridine ligand). The new derivatives bearing the ferrocenyl diphosphine are active at a slightly higher temperature with respect to the analogous complexes with dppb showing an alkyl backbone. The studies on (*S*)-1-phenylethanol reveal that the deuteration occurs with simultaneous racemization, suggesting that both reactions involve an oxido-reductive process through formation of the corresponding ketone. Work is in progress to shed light on the mechanism of these transformations and improve the design of more efficient catalysis for the activation of alcohol C–H bonds.

Experimental

General comments

All reactions were carried out under an argon atmosphere using standard Schlenk techniques. The solvents were carefully dried by standard methods and distilled under argon before use. The diphosphanes and all other chemicals were purchased from Aldrich and Strem and used without further purification. The compounds [$MCl_2(PPh_3)_3$] (M = Ru,[28] Os[29]), [$RuCl_2(PPh_3)$(dppb)],[22] **1**,[8f] **5**[8d] and **8**[8d] were prepared according to the literature procedure. NMR measurements were recorded on a Bruker AC 200 spectrometer and the chemical shifts, in ppm, are relative to TMS for ^{1}H and ^{13}C{^{1}H}, and 85% H_3PO_4 for ^{31}P{^{1}H}. Elemental analyses (C, H, N) were carried out with a Carlo Erba 1106 elemental analyzer, whereas the GC analyses were performed with a Varian GP-3380 gas chromatograph equipped with a MEGADEX-ETTBDMS-β chiral column.

Preparation of the pincer complexes

Ru complex 2. [$RuCl_2(PPh_3)$(dppb)] (250 mg, 0.290 mmol), NEt_3 (405 μL, 2.90 mmol) and *rac*-1-(6-phenylpyridin-2-yl)ethanamine (70 mg, 0.353 mmol) were suspended in 2-propanol (4.0 mL) and the mixture was refluxed for 3 h, obtaining a yellow precipitate. After filtration the product was washed with methanol (3 × 1 mL) and dried under reduced pressure (180 mg, 82%). Found: C, 64.45; H, 5.21; N, 3.43. Calc. for $C_{41}H_{41}ClN_2P_2Ru$: C, 64.77; H, 5.44; N, 3.68. ^{1}H NMR (200.1 MHz; CD_2Cl_2) δ 8.12 (2H, dt, J_{HH} = 8.1 and 1.7 Hz, aromatic protons), 7.84 (3H, dt, J_{HH} = 8.2 and 1.4 Hz, aromatic protons), 7.44–6.78 (17H, m, aromatic protons), 6.60 (3H, dt, J_{HH} = 7.6 and 1.8 Hz, aromatic protons), 5.93 (2H, t, J_{HH} = 8.5 Hz, aromatic protons), 3.75 (1H, m, C*H*N), 3.47 (1H, m, NH_2), 3.08 (2H, m, CH_2P), 2.40–1.60 (7H, m, NH_2 and CH_2), 1.44 (3H, d, J_{HH} = 6.6 Hz, CH_3). ^{13}C{^{1}H} NMR (50.3 MHz; CD_2Cl_2) δ 181.9 (dd, J_{CP} = 16.3 and 7.6 Hz, CRu), 163.7 (s, N*C*C), 158.3 (s, N*C*CH), 149.3–116.1 (m, aromatic carbons), 57.4 (d, J_{CP} = 2.7 Hz, CHN), 32.9 (d, J_{CP} = 24.5 Hz, CH_2P), 30.3 (d, J_{CP} = 31.7 Hz, CH_2P), 26.4 (s, CH_2), 23.0 (s, CH_3), 21.5 (s, CH_2). ^{31}P{^{1}H} NMR (81.0 MHz; CD_2Cl_2) δ 57.4 (d, J_{PP} = 38.7 Hz), 42.1 (d, J_{PP} = 38.7 Hz).

Ru complex 3. Compound **2** (150 mg, 0.197 mol) was dissolved in dichloromethane (5 mL) and thallium triflate (73 mg, 0.207 mol) was added. The orange suspension was stirred at room temperature for 4h, filtered on Celite to eliminate TlCl and the solution was reduced to 1 mL. Addition of heptane afforded a yellow precipitate, which was filtered, washed with heptane and dried under reduced pressure (143 mg, 83%). Found: C, 57.45; H, 4.70; N, 3.11. Calc. for $C_{42}H_{41}F_3N_2O_3P_2RuS$: C, 57.73; H, 4.73; N, 3.21. ^{1}H NMR (200.1 MHz; CD_2Cl_2) δ 7.91 (2H, m, aromatic protons), 7.70–6.71 (23H, m, aromatic protons), 5.98 (2H, m, aromatic protons), 3.78 (1H, m, C*H*N), 3.47 (1H, m, NH_2), 3.05 (2H, m, CH_2P), 2.39–1.60 (7H, m, NH_2 and CH_2), 1.46 (3H, d, J_{HH} = 6.4 Hz, CH_3). ^{13}C{^{1}H} NMR (50.3 MHz; CD_2Cl_2) δ 179.1 (s, CRu), 164.6 (s, N*C*C), 161.0 (s, N*C*CH), 150.6–116.9 (m, aromatic carbons and CF_3), 58.5 (d, J_{CP} = 2.0 Hz, CHN), 31.6 (d, J_{CP} = 34.9 Hz, CH_2P), 31.2 (d, J_{CP} = 24.8 Hz, CH_2P), 26.3 (s, CH_2), 23.9 (s, CH_3), 21.7 (s, CH_2). ^{31}P{^{1}H} NMR (81.0 MHz; CD_2Cl_2) δ 66.0 (br s), 42.1 (br s). ^{19}F NMR (188.3 MHz; CD_2Cl_2) δ –77.6 (s).

Ru complex 4. [$RuCl_2(PPh_3)_3$] (100 mg, 0.104 mmol) and dppf (64 mg, 0.115 mmol) were dissolved in dichloromethane (1.5 mL) and the solution was stirred for 2 h at room temperature. The solvent was evaporated under reduced pressure and 1-[6-(4′-methylphenyl)pyridin-2-yl]methanamine (26 mg, 0.131 mmol) dissolved in 2-propanol (3 mL) and NEt_3 (145 μL, 1.04 mmol) were added. The mixture was refluxed for 3 h obtaining a yellow precipitate which was filtered, washed with 2-propanol (3 × 1 mL),

heptane (3 × 1 mL) and dried under reduced pressure (75 mg, 81%). Found: C, 63.11; H, 4.41; N, 3.11. Calc. for $C_{47}H_{41}ClFeN_2P_2Ru$: C, 63.56; H, 4.65; N, 3.15. ^{1}H NMR (200.1 MHz; CD_2Cl_2) δ 8.47 (2H, dt, J_{HH} = 8.6 and 1.4 Hz, aromatic protons), 8.22 (1H, s, aromatic proton), 7.96 (2H, dt, J_{HH} = 8.1 and 1.8 Hz, aromatic protons), 7.72–6.62 (19H, m, aromatic protons), 6.42 (2H, dt, J_{HH} = 8.4 and 1.3 Hz, aromatic protons), 5.24 (1H, m, C_5H_4), 4.84 (1H, m, C_5H_4), 4.33 (1H, m, C_5H_4), 4.21 (1H, m, C_5H_4), 4.17 (1H, m, C_5H_4), 4.09 (1H, m, NH_2), 3.99 (1H, m, C_5H_4), 3.84 (1H, m, C_5H_4), 3.51 (2H, m, CH_2), 3.16 (1H, m, C_5H_4), 2.32 (3H, s, CH_3), 2.04 (1H, m, NH_2). ^{13}C{^{1}H} NMR (50.3 MHz; CD_2Cl_2) δ 182.7 (s, CRu), 163.7 (s, N*C*C), 157.1 (s, N*C*CH_2), 150.6–115.9 (m, aromatic carbons), 77.4 (d, J_{CP} = 13.4 Hz, C_5H_4), 76.9 (d, J_{CP} = 7.8 Hz; C_5H_4), 75.7 (d, J_{CP} = 2.9 Hz; C_5H_4), 73.9 (d, J_{CP} = 6.9 Hz; C_5H_4), 73.3 (d, J_{CP} = 4.8 Hz, C_5H_4), 69.5 (d, J_{CP} = 5.0 Hz, C_5H_4), 69.3 (d, J_{CP} = 3.3 Hz, C_5H_4), 68.9 (d, J_{CP} = 5.2 Hz, C_5H_4), 51.6 (s, CH_2), 21.6 (s, CH_3). ^{31}P{^{1}H} NMR (81.0 MHz; CD_2Cl_2) δ 62.4 (d, J_{PP} = 36.0 Hz), 45.1 (d, J_{PP} = 36.0 Hz).

Os complex 6. $[OsCl_2(PPh_3)_3]$ (300 mg, 0.286 mmol) and dppb (146 mg, 0.342 mmol) were dissolved in dichloromethane (4 mL) and the solution was stirred for 3 h at room temperature. The solvent was evaporated under reduced pressure and *rac*-1-(6-phenylpyridin-2-yl)ethanamine (71 mg, 0.358 mmol) dissolved in 2-propanol (3 mL) and NEt_3 (400 µL, 2.87 mmol) were added. The mixture was refluxed for 3 h obtaining a red precipitate which was filtered, washed with 2-propanol (3 × 3 mL), heptane (3 × 1 mL) and dried under reduced pressure (218 mg, 90%). Found: C, 57.95; H, 4.91; N, 3.43. Calc. for $C_{41}H_{41}ClN_2OsP_2$: C, 57.98; H, 4.87; N, 3.30. ^{1}H NMR (200.1 MHz; CD_2Cl_2) δ 7.98 (2H, m, aromatic protons), 7.70 (3H, m, aromatic protons), 7.46–6.76 (17H, m, aromatic protons), 6.61 (3H, m, aromatic protons), 5.93 (2H, t, J_{HH} = 7.9 Hz, aromatic protons), 3.69 (1H, m, NH_2), 3.49 (1H, m, C*H*NH_2), 3.06 (2H, m, CH_2P), 2.47 (2H, m, CH_2P), 1.95–1.80 (5H, m, CH_2 and NH_2), 1.55 (3H, d, J_{HH} = 5.6 Hz, CH_3). ^{13}C{^{1}H} NMR (50.3 MHz; CD_2Cl_2) δ 166.1 (s, N*C*C), 162.5 (dd, J_{CP} = 5.7 and 2.5 Hz, OsC), 159.3 (s, N*C*CH), 148.0–116.6 (m, aromatic carbons), 60.3 (s, $CHNH_2$), 35.3 (d, J_{CP} = 5.0 Hz, CH_2P), 30.9 (d, J_{CP} = 5.1 Hz, CH_2P), 26.5 (s, CH_2), 23.0 (s, CH_3), 21.2 (s, CH_2). ^{31}P{^{1}H} NMR (81.0 MHz; CD_2Cl_2) δ 0.28 (s).

Os complex 7. $[OsCl_2(PPh_3)_3]$ (100 mg, 0.095 mmol) and dppf (58 mg, 0.105 mmol) were dissolved in dichloromethane (1.5 mL) and the solution was stirred for 2 h at room temperature. The solvent was evaporated under reduced pressure and 1-[6-(4′-methylphenyl)pyridin-2-yl]methanamine (24 mg, 0.121 mmol) dissolved in 2-propanol (3 mL) and NEt_3 (132 µL, 0.95 mmol) were added. The mixture was refluxed for 3 h obtaining a red precipitate which was filtered, washed with 2-propanol (3 × 1 mL), heptane (3 × 1 mL) and dried under reduced pressure (72 mg, 78%). Found: C, 57.42; H, 4.03; N, 2.88. Calc. for $C_{47}H_{41}ClFeN_2OsP_2$: C, 57.76; H, 4.23; N, 2.87. ^{1}H NMR (200.1 MHz; CD_2Cl_2) δ 8.36 (2H, t, J_{HH} = 8.2 Hz, aromatic protons), 8.15 (1H, s, aromatic proton), 7.90 (2H, t, J_{HH} = 7.7 Hz, aromatic protons), 7.66–6.64 (19H, m, aromatic protons), 6.44 (2H, t, J_{HH} = 8.4 Hz, aromatic protons), 5.22 (1H, s, C_5H_4), 4.81 (1H, s, C_5H_4), 4.30 (1H, s, C_5H_4), 4.15 (2H, s, C_5H_4), 4.05 (1H, broad s, NH_2), 3.99 (1H, s, C_5H_4), 3.80 (1H, s, C_5H_4), 3.44 (1H, m, CH_2), 3.10 (1H, s, C_5H_4), 2.77 (1H, m, CH_2), 2.33 (3H, s, CH_3), 1.53 (1H, s, NH_2). ^{13}C{^{1}H} NMR (50.3 MHz; CD_2Cl_2) δ 165.9 (s, N*C*C), 159.6 (s, OsC), 157.5 (s, N*C*CH_2), 150.5–115.9 (m, aromatic carbons), 88.6 (d, J_{CP} = 46.5 Hz, *ipso*-C_5H_4), 87.2 (d, J_{CP} = 58.2 Hz, *ipso*-C_5H_4), 77.2 (s; C_5H_4), 76.9 (s, C_5H_4), 76.8 (s, C_5H_4), 76.2 (d, J_{CP} = 3.6 Hz, C_5H_4), 73.5 (d, J_{CP} = 7.3 Hz, C_5H_4), 73.2 (d, J_{CP} = 5.0 Hz, C_5H_4), 69.5 (d, J_{CP} = 5.5 Hz, C_5H_4), 69.0 (s, C_5H_4), 53.9 (s, CH_2), 21.5 (s, CH_3). ^{31}P{^{1}H} NMR (81.0 MHz; CD_2Cl_2) δ 4.6 (d, J_{PP} = 20.2 Hz), 0.7 (d, J_{PP} = 20.2 Hz).

General procedure for the racemization of alcohols. The catalyst (1.6 µmol) and KO*t*Bu (8.2 µmol) were dissolved in 2-propanol (0.5 mL) and the chiral alcohol (0.164 mmol) was added under argon. The solution was stirred at the desired temperature and monitored over time by taking aliquots (25 µL) that were filtered over a short pad of silica (eluent: diethyl ether) and analyzed by chiral GC.

General procedure for deuteration of alcohols. In a NMR tube the catalyst (1.6 µmol) and KO*t*Bu (8.2 µmol) were dissolved in 2-propanol-d_8 (0.5 mL) and the substrate (0.164 mmol) was added under argon. The solution was kept under the desired temperature and the incorporation of D content was monitored over time by NMR spectroscopy. In the case of (*S*)-1-phenylethanol, the solution was also analyzed by chiral GC, according to the above procedure for the racemization of alcohols (2-propanol-d_8/substrate = 40).

Preparation of 1-phenylethanol-d_5. The osmium complex **5** (4.3 mg, 5.0 µmol) and KO*t*Bu (2.8 mg, 25 µmol) were dissolved in 2-propanol-d_8 (1.5 mL) and 1-phenylethanol (122 mg, 1.00 mmol) was added under argon. The solution was stirred at 40 °C for 5 h and the solvent was evaporated under reduced pressure. After addition of 2-propanol-d_8 (1.5 mL) the solution was stirred for 5 h (40 °C). Diethyl ether (2 mL) was added and the solution was filtered over a short pad of silica, which was washed with diethyl ether (4 mL). The mixture of solvents was evaporated at about 45 °C, affording 1-phenylethanol-d_5 (110 mg, 87% yield) (0.5 mol% of **5** and 2.5 mol% of KO*t*Bu).

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X

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