Ruthenium and osmium complexes containing 2-(aminomethyl)pyridine (Ampy)-based ligands in catalysis

Ruthenium and Osmium complexes containing 2-(aminomethyl)pyridine (Ampy)-based ligands in catalysis

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Abstract

This account focuses on the application in catalysis of ruthenium and osmium complexes containing 1-(pyridin-2-yl)methanamine (Ampy)- based ligands. The combination of these aminoalkylpyridine ligands with appropriate phosphines affords ruthenium and osmium systems displaying unprecedented high catalytic activity and productivity in a variety of organic transformations such as hydrogenation by hydrogen transfer and dihydrogen, dehydrogenation, racemization, alkylation, etc.

1. Introduction

The search for highly efficient transition-metal homogeneous catalysts is a current issue of industrial relevance for the synthesis of valuable organic compounds. In this context, ruthenium [1] and more recently osmium complexes [2] are among the preferred metals because of their high performance and versatility in a variety of processes. High productivity and selectivity, which are crucial parameters in catalysis, can be achieved through an appropriate ligand design, resulting in the formation of structurally well-defined catalysts. Nevertheless, there is also a great interest in multitasking catalysts able to efficiently promote different organic transformations by a careful switching of the reaction

parameters such as temperature, solvent and co-catalyst. Moreover, to make catalysts appealing for industrial applications, their high productivity, robustness and easy availability are the prerequisite s. In the area of metal-complexes catalyzed transformations, pyridine-based ligands are playing an important role because of their ability to form complexes with several metals in different oxidation states [3]. In this contest 2-(aminomethyl)pyridine (Ampy) type ligands, have attracted a large interest in the last decade, leading to the development of a new generation of catalysts with high performances [4,5].

In this account, we summarize our and others efforts toward the designing of a new class of ruthenium and osmium complexes, based on the Ampy motif, which in combination with appropriate phosphines lead to highly active catalysts capable to promote a variety of organic transformations such as hydrogenation by hydrogen transfer and dihydrogen, dehydrogenation, racemization, deuteration and alkylation.

The present review is organized according to the category of the metal-catalyzed reaction, and each of these processes is arranged, where possible, according to the used metal complex, namely, ruthenium or osmium.

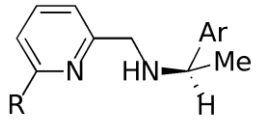
2. Hydrogenation by hydrogen transfer of aldehydes and ketones

Catalytic transfer hydrogenation (TH) is a convenient method to reduce carbonyl compounds to the corresponding alcohols without the use of hazardous hydrogen gas or moisture-sensitive hydride reagents [6]. Moreover, the TH of ketones is widely accepted in industry as a cost-effective and environmentally benign way for the production of a number of hydroxylated organic products [7]. A crucial improvement in the development of highly active metal systems for the reduction of carbonyl compounds was given by Noyori and co-workers who observed that NH_2 amine ligands in Ru based complexes accelerate the catalytic hydrogenation (HY) [8] and TH of simple ketones [9]. Thus, the catalyst (η^6-arene) $RuCl(TsNCHPhCHPhNH_2)$ (Ts = $SO_2C_6H_4CH_3$), displaying the N−H function, paved the way for the growth of more efficient catalysts for carbonyl compound TH [10]. Evidence has been provided that the *cis*-Ru-H/-NH_2 motif plays a fundamental role in catalysis through a concerted delivery of a N-H proton and a Ru-H hydride, via an outer sphere mechanism (metal-ligand bifunctional catalysis) [11]. The 2-(aminomethyl)pyridine (Ampy) based ligands were reported by Brunner in the 80' and employed for the in situ formation of rhodium catalysts in the asymmetric hydrosilylation of ketones [12]. Yamagishi and co-workers described in late '90 the use in TH of *in situ* formed ruthenium complexes containing Ampy based ligands ~~and~~ in combination with phosphine ligands [13]. After this pioneering work, a number of ruthenium and more recently osmium complexes based on the Ampy moiety have been developed and are now playing a central role in this catalytic process.

2.1. Ruthenium complexes

2.1.1. Bidentate NN Ampy-based ruthenium complexes.

Yamagishi and co-workers first described the use of Ru-complexes having both Ampy derivatives and phosphine ligands for the asymmetric transfer hydrogenation (ATH) of ketones [13]. Ru(II)- complexes generated *in situ* from aminomethylpyridines **1a**–**c** (Fig. 1) and $RuCl_2(PPh_3)_3$, $RuHCl(PPh_3)_3$ or $RuH_2(PPh_3)_4$ were examined in the ATH of 1-acetonaphthone with propan-2-ol as hydrogen donor and KOH as co-catalyst. With the catalyst formed by **1a** (4 mol%), $RuCl_2(PPh_3)_3$ (1 mol%) and KOH (5 mol%) at 85 °C, (*R*)-1-(naphthalen-1-yl)ethanol was obtained in 77% yield and with 45% ee (Scheme 1). Under these reaction conditions other aromatic ketones were converted into the related alcohols in up to 99% yield and 58% ee. These ligands (5 mol%) were also used in combination with $RuHCl(PPh_3)_3$ (1 mol%) in the ATH of aromatic ketones by using $HCOOH/NEt_3$ as hydrogen donor. With this catalytic system, activities and enantioselectivities were much improved, reaching with **1a** yields and enantiomeric excesses up to 100% and 86%, respectively (Scheme 2).

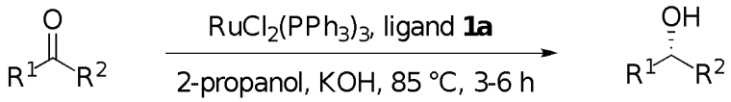


1a-c

a: R = H, Ar = Ph, **b**: R = H, Ar = 1-naphthyl
c: R = Me, Ar = Ph

Fig. 1. Chemical structure of the ligands **1a**–**c**.

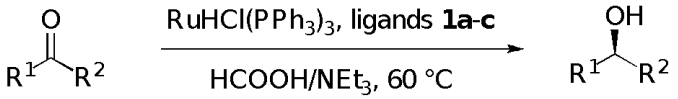
Se puoi metti la linea del 1-naphtyl come prima linea



R^1	R^2	time (h)	yield (%)	ee (%)
Ph	Me	6	98	31
Ph	Et	6	99	42
Ph	*i*-Pr	6	91	58
Ph	*i*-Bu	3	74	51
1-naphthyl	Me	3	77	45

Reaction conditions: $RuCl_2(PPh_3)_3$ (1 mol%), ligand (4 mol%) and KOH (5 mol%) at 85 °C.

Scheme 1. ATH of aromatic ketones catalyzed by $RuCl_2(PPh_3)_3$/**1a**.



R^1	R^2	ligand	time (h)	yield (%)	ee (%)
Ph	Me	**1a**	48	93	59
Ph	Et	**1a**	66	83	73
Ph	*i*-Pr	**1a**	120	100	86
Ph	*i*-Bu	**1b**	90	100	76
1-naphthyl	Me	**1a**	70	100	57
Ph	Bn	**1a**	120	31	67
Ph	Bn	**1b**	61	100	64
Ph	Cy	**1a**	40	78	81
Ph	Cy	**1b**	89	100	80
Ph	Cy	**1c**	85	37	50

Only representative examples are reported. Reaction conditions: $RuHCl(PPh_3)_3$ (1 mol%), ligand (5 mol%) at 60 °C.

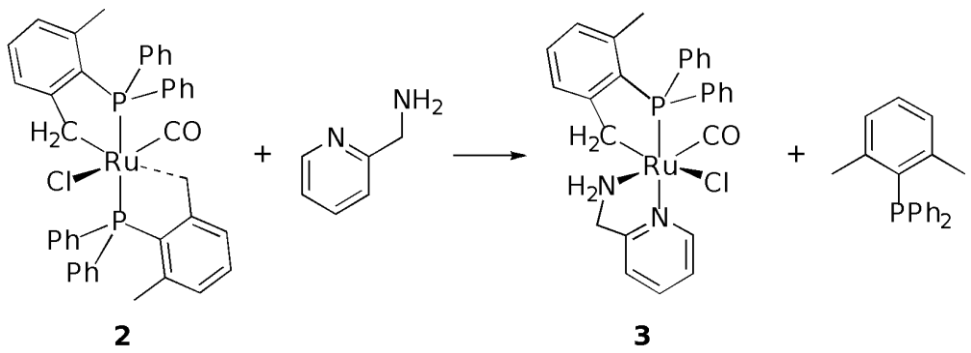
Scheme 2. ATH of aromatic ketones catalyzed by $RuHCl(PPh_3)_3$/**1a**–**c**.

The Yamagishi studies on the ATH using *in situ* generated Ru-species with Ampy derivatives showed the efficiency of this type of ligands, but the potential of the simpler exponent of this family, namely 1-(pyridin-2-yl)methanamine (Ampy) in TH was not recognized.

Our research on the TH of ketones began with the study of the reactivity of the 16-electron monocarbonyl complex $RuCl[(2\text{-}CH_2\text{-}6\text{-}MeC_6H_3)PPh_2](CO)[(2,6\text{-}Me_2C_6H_3)PPh_2]$ (**2**) [14] in which one phosphine is cyclometalated, while the other one shows one methyl group that interacts with the metal in an agostic fashion (Scheme 3). This compound appeared to be a good precursor for catalytic TH studies because of the presence of a chloride that can be converted into the related hydride during catalysis, and of a weakly coordinated bulky phosphine occupying two coordination sites that can easily be displaced by two mono or a bidentate phosphorus or nitrogen containing ligands, affording a large number of cyclometalated complexes of formula $RuCl[(2\text{-}CH_2\text{-}6\text{-}MeC_6H_3)PPh_2](CO)L_2$ (L = monodentate or L_2 = bidentate ligand). These complexes were quickly generated *in situ* and then directly assessed in TH, thus reducing the time necessary for the search of the most favorable combination of ligands.

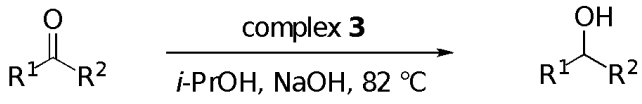
Among the examind ligands a remarkable result was obtained through the combination of **2** with Ampy, which afforded complete conversion of acetophenone in 5 min (TOF = 6.0×10^4 h^{-1}) with 0.05 mol% Ru, thus showing to be one of the most active system reported at that time [14]. At 0.01 mol% loading of the **2**-Ampy system complete conversion of acetophenone was also achieved in less than 1 h, suggesting that the catalytically active species is relatively robust (i.e. deactivation occurred slowly), on account of the presence of the cyclometalated phosphine. Without base, the system **2**-Ampy was

practically not active, suggesting that during catalysis in the basic alcohol media the Ru-chloride is converted into hydride and alkoxide species. It is worth noting that the use of the related ligand 2-(pyridin-2-yl)ethanamine (with a $–CH_2CH_2-$ spacer instead of CH_2 between the pyridine ring and the amino group) resulted in a much less active system (TOF of about 4×10^3 h^{-1}), indicating that the chain length is crucial for the catalyst activity. Thus, the complex **3** was isolated by reaction of **2** with an equimolar amount of Ampy, and its structure was established in solution through a Roesy NMR experiment (Scheme 3) [15]. Compound **3** displayed the same activity of **2**-Ampy, catalyzing the quantitative TH of a large number of aliphatic (linear and cyclic) and aromatic ketones within few minutes with TOF up to 6.3 x 10^4 h^{-1}. Examples in Scheme 4 show that the chemoselective C=O reduction was also observed for olefinic ketones such as 5-hexen-2-one for which no C=C reduction or isomerization occurred. Diaryl ketones, which are substrates difficult to reduce, were converted to benzhydrols even at low loading of catalyst (0.01 mol%, 2 h), indicating that TH is a valid alternative to HY for the synthesis of alcohols. Interestingly, also bulky ketones, such 3,3-dimethyl-2-butanone, 2,2-dimethylpropiophenone and (-)-menthone were reduced quantitatively to alcohols (TOF /10^4 = 0.9–2.0 h^{-1}). We ascribed the lower rate observed in the latter case to the high steric crowding of the ketone that impedes the access to the metal center. We attributed the robustness of the system **3** to the strong Ru-carbon bond that was apparently not cleaved under catalytic basic conditions. This is a fundamental point because in order to achieve efficient catalysts, it is necessary that the system shows a high rate at the beginning and survives for a long period to obtain high productivity. As a matter of fact, many TH systems are active at relatively high catalyst loading (1–0.1 mol%) and cannot be employed in lower amount due to their facile deactivation, namely for the presence of oxygen or side products in the solvent or the substrate, limiting their application for the preparation of alcohols. The superior performance of the ligand Ampy respect to diamines (e.g. $H_2N(CH_2)_2NH_2$) may be ascribed to the combination of the NH effect with the flat geometry of the pyridine that allows easy access of the substrate, even bulky, to the metal center.



2 **3**

Scheme 3. Synthesis of the Ru-complex **3**.

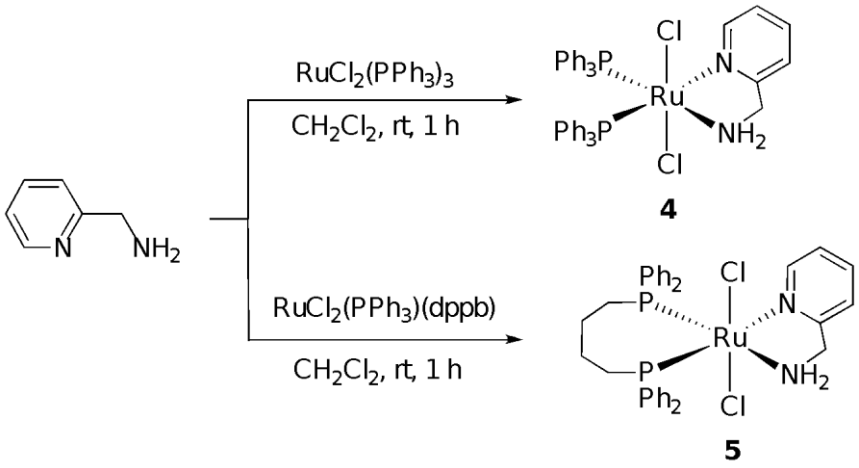


R^1	R^2	conv (%)	time (min)	TOF(h^{-1})
Ph	Me	98	5	6.0×10^4
2-ClC_6H_4	Me	99	10	2.9×10^4
n-C_4H_9	Me	99	10	6.3×10^4
CH_2=$CHCH_2CH_2$	Me	95	10	3.0×10^4
-$CH_2(CH_2)_2CH_2$-		99	10	3.4×10^4
-$CH_2(CH_2)_2CH_2$-		99	15	1.9×10^4
Ph	Ph	95	5	3.6×10^4
4-ClC_6H_4	4-ClC_6H_4	98	10	1.8×10^4

Reaction conditions: ketones (0.1 M), complex (0.05 mol%) and NaOH (2 mol%) in 2-propanol at 82 °C.

Scheme 4. TH of ketones catalyzed by the Ru-complex **3**.

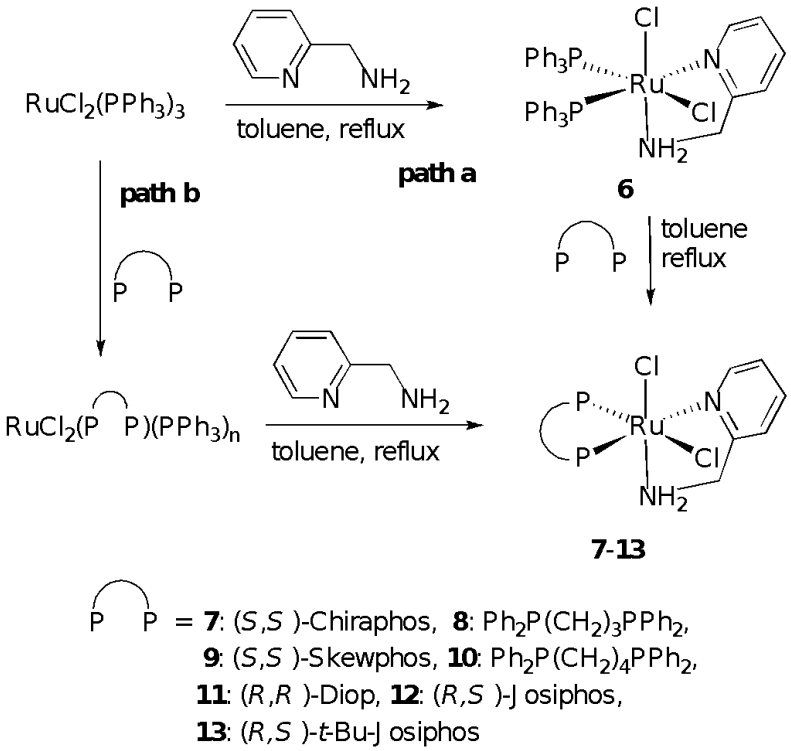
The excellent catalytic performance of the Ampy-based cyclometalated Ru compound **3** prompted us to develop new Ru-Ampy catalysts. One of the most well-known Ru-precursor is $RuCl_2(PPh_3)_3$ which can easily react with phosphorus and nitrogen ligands by displacement of PPh_3 [16]. Since, preliminary catalytic results showed that the *in situ* prepared $RuCl_2(PPh_3)_3$/Ampy system is catalytically active in the TH of acetophenone, a series of complexes of general formula $RuCl_2P_2$(Ampy) (P = phosphine or P_2 = diphosphine) were prepared ~~[18]~~ [17]. At room temperature the precursors $RuCl_2(PPh_3)_3$ and $RuCl_2(PPh_3)$(dppb) (dppb = $Ph_2P(CH_2)_4PPh_2$) reacted with Ampy, affording the derivatives *trans*-$RuCl_2(PPh_3)_2$(Ampy) **4** and *trans*-$RuCl_2$(dppb)(Ampy) **5**, respectively (Scheme 5).



Scheme 5. Synthesis of the Ru-complexes **4** and **5**.

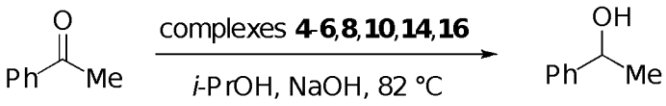
The thermodynamically most stable complexes *cis*-$RuCl_2P_2$(Ampy) were obtained by treatment of $RuCl_2(PPh_3)_3$ with Ampy in toluene at reflux and addition of a suitable achiral or chiral diphosphine,

namely $Ph_2P(CH_2)_nPPh_2$ (n = 3,4), (*S*,*S*)-Chiraphos, (*S*,*S*)-Skewphos and (*R*,*R*)-Diop (path a, Scheme 6). With bulky phosphines, (*R*,*S*)-Josiphos and (*R*,*S*)-*t*-Bu-Josiphos, these Ampy compounds could be obtained by reversing the order of the reactants (path b, Scheme 6). It is worth noting that with the optically active diphosphines a single stereoisomer was formed in solution, as inferred from NMR spectroscopy.



Scheme 6. Synthesis of the Ru-complexes **6**–**13**.

Compounds $RuCl_2P_2$(Ampy) **4**–**6**,**8** and **10** displayed good to very high catalytic activity in TH of ketones in 2-propanol at reflux and in the presence of NaOH (Scheme 7). The *cis* complexes proved to be more active than the corresponding *trans* isomers and the best performances were obtained with diphosphine ligands. For example *cis*-$RuCl_2$(dppb)(Ampy) **10** at 0.05 mol% catalyzes the quantitative TH of acetophenone in 1 min with a TOF = 3.0×10^5 h^{-1} (Scheme 7).



complex	conv (%)	time (min)	TOF (h^{-1})
4	83	90	2.4×10^3
5	98	10	3.5×10^4
6	98	70	5.2×10^3
8	97	1	2.2×10^5
10	97	1	3.0×10^5
14	98	10	2.8×10^4
16	92	30	1.1×10^4

Reaction conditions: acetophenone (0.1 M) in 2-propanol, complex (0.05 mol%) and NaOH (2 mol%) at 82 °C.

Scheme 7. TH of acetophenone catalyzed by the Ru-complexes **4**-**6**,**8**,**10**,**14** and **16**.

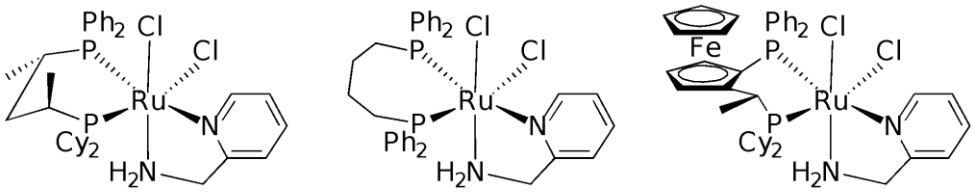
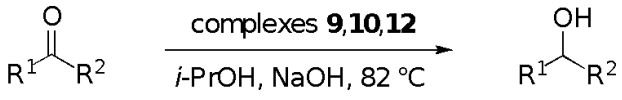


Fig. 2. Chemical structures of the Ru-complexes **9**,**10** and **12**.

With **10** numerous ketones, such as cyclohexanone, 5-hexen-2-one and benzophenone were quantitatively and chemoselectively reduced to the corresponding alcohols within 10 min and with TOF up to 4.0×10^5 h^{-1}, which was the highest value reported at that time (Scheme 8) ~~[18]~~ [17] .



complex	R^1	R^2	conv (%)	time (min)	TOF (h^{-1})	ee (%) (conf)
10	$-CH_2(CH_2)_3CH_2-$		99	1	4.0×10^5	
10	$-CH_2(CH_2)_2CH_2-$		97	5	8.8×10^4	
10	$CH_2{=}CHCH_2CH_2$	Me	94	10	2.8×10^5	
10	Ph	Ph	98	10	8.0×10^4	
9	Ph	Me	96	1	3.0×10^5	85 (*S*)
12	Ph	Me	97	2	2.3×10^5	83 (*R*)
9	2-ClC_6H_4	Me	96	1	2.9×10^5	89 (*S*)
9	2-$MeOC_6H_4$	Me	96	2	2.5×10^5	94 (*S*)
9	2-pyridyl	Ph	98	5	1.5×10^5	90 (*S*)

Reaction conditions: ketones (0.1 M), complex (0.05 mol%), NaOH (2 mol%) in 2-propanol at 82 °C.

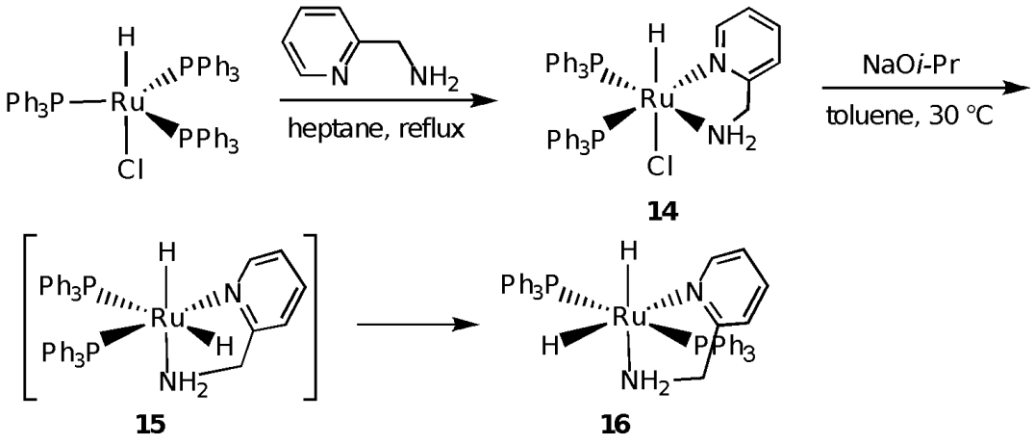
Scheme 8. TH of ketones catalyzed by the Ru-complexes **9**,**10** and **12**.

Fast ATH of methyl aryl ketones was observed by using the chiral derivative *cis*-$RuCl_2$[(*S*,*S*)-Skewphos](Ampy) **9** (Fig. 2). Thus, acetophenone was reduced with **9** (0.05 mol% at 82 °C) to (*S*)-1-phenylethanol in 1 min (TOF = 3.0×10^5 h^{-1}) with 85% *ee*; no erosion of enantioselectivity occurred at lower catalyst loading (0.01 mol%). The o*rtho* substituted ketones 1-(2-chlorophenyl)ethanone and 1-(2-methoxyphenyl)ethanone were quickly reduced to the corresponding (*S*)-alcohols with *ee* up to 94%, whereas (*S*)-phenyl(pyridin-2-yl)methanol was obtained with 90% ee from the corresponding pyridyl ketone. The employment of *cis*-$RuCl_2$[(*R*,*S*)-Josiphos](Ampy) (**12**) (Fig. 2) resulted in TH of acetophenone to (*R*)-1-phenylethanol in 2 min with 83% ee.

Since $RuCl_2P_2$(Ampy) were not active in TH without base, we decided to prepare the mono and dihydride complexes of the type $RuH_nCl_{2-n}(PPh_3)_2$(Ampy) (n = 1, 2). Thus, the compound *trans,cis*-$RuHCl(PPh_3)_2$(Ampy) **14** was prepared from $RuHCl(PPh_3)_3$ and Ampy in refluxing heptane (Scheme 9). When compound **14** was treated with an equimolar amount of NaO*i*-Pr in toluene, the derivative *cis*,*trans*-$Ru(H)_2(PPh_3)_2$(Ampy) **16**, showing two *trans* phosphorus atoms, was formed at 30 °C within few hours.

Under the usual experimental conditions both hydride derivatives **14** and **16** were capable of reducing efficiently acetophenone with 2-propanol by addition of base (Scheme 7), while the dihydride **16** was catalytically active in the reduction of acetophenone also without base (TOF = 5.5×10^3 h^{-1}). NMR studies showed that during the synthesis of **16**, the dihydride intermediate *cis*,*cis*-$Ru(H)_2(PPh_3)_2$(Ampy) **15** forms and slowly converts into the final product (Scheme 9). This indicates

that during catalysis the dichloride complexes $RuCl_2P_2$(Ampy) react with NaO*i*-Pr, affording mono- and di-hydride species, whose activity in the TH depends on the type of geometry of the complex.

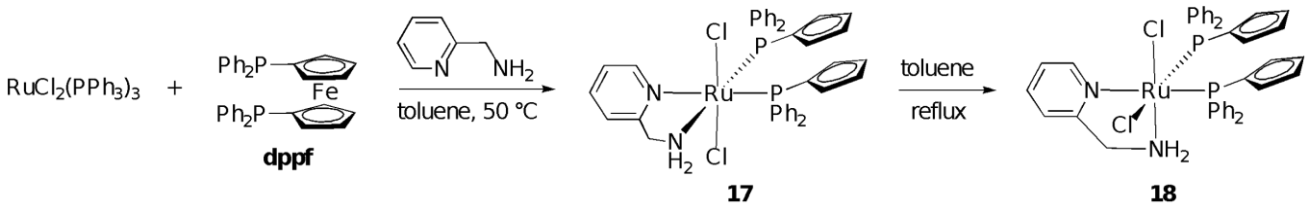


Scheme 9.

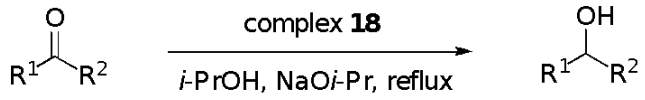
Synthesis of hydride Ru-complexes **14** and **16**.

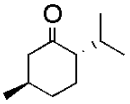
We recently prepared the derivative *cis*-$RuCl_2$(dppf)(ampy) **18** (Scheme 10) which was found to catalyze a variety of organic transformations involving ketones and alcohols [18]. Treatment of $RuCl_2(PPh_3)_3$ with 1,1-bis(diphenylphosphino)ferrocene (dppf) and Ampy in toluene at 50 °C gave in 92% yield the derivative **17** with *trans*-configuration, which by heating in toluene at reflux temperature for 24 h afforded the thermodynamically more stable *cis*-isomer **18** (Scheme 10) [19]. The Ru-complex **18** catalyzed efficiently the selective TH of aldehydes and ketones to alcohols [18]. By using a catalyst loading of 0.1−0.0005 mol% and in the presence of NaO*i*-Pr (2 mol%) in 2-propanol, quantitative conversion of several carbonyl compounds was achieved at 82 °C in a short time, affording TOF up to 1.0×10^5 h^{-1} (Scheme 11).

Scrivere NH2 per il complesso **18**



Scheme 10. Synthesis of the Ru-complexes **17** and **18**.



R^1	R^2	conv (%)	time (h)	TOF (h^{-1})
Ph	H	96	2	2.8×10^4
4-$MeOC_6H_4$	H	96	1	5.4×10^4
n-C_5H_{11}	H	94[a]	5 min	2.6×10^4
$C_2H_5(CH_3)CH$	H	99	10 min	1.0×10^5
$(CH_3)_2C{=}CH(CH_2)_2CH(CH_3)CH_2$	H	87[a]	2	2.4×10^3
PhCH=CH	H	75	20	1.8×10^4
Ph	Me	95[a]	30 min	1.5×10^4
4-$MeOC_6H_4$	Me	85[b]	30 min	5.0×10^4
Ph	*t*-Bu	90[a]	1	2.2×10^3
Ph	Ph	96	2	7.2×10^4
$CH_2{=}CHCH_2CH_2$	Me	90[a]	30	2.8×10^4
		96[a]	30 min	4.6×10^4

Reaction conditions: carbonyl compound (0.1 M), Ru-complex (0.005 mol%) with NaO*i*-Pr (2.0 mol%) in 2-propanol at reflux temperature. [a]Ru-complex (0.05 mol%). [b]Ru-complex (0.1 mol%)

Scheme 11. TH of aldehydes or ketones catalyzed by the Ru-complex **18**.

As regards the asymmetric reduction of carbonyl compounds, a high level of enantioselectivity was achieved in hydrogenation with the well-known Noyori catalysts *trans*-$RuCl_2$(PP)(1,2-diamine), through the correct matching of the PP and NN chiral ligands [20]. For these catalysts, the search of the suitable ligand combination is a relatively tedious approach and requires the isolation of a library of precious enantiomerically pure ligands. To overcome this problem, different strategies have been developed, including the reaction of a racemic metal complex with a suitable chiral ligand, leading to deactivation (chiral poisoning) or activation of one metal enantiomeric species [21]. For the asymmetric TH catalyzed by *cis*-$RuCl_2$(PP)(Ampy) based complexes, a further improvement was achieved by isolation the derivatives *cis*-$RuCl_2$(PP)(RAmpy) containing a chiral diphosphine (PP) correctly matched with a chiral 1-substituted Ampy (RAmpy).

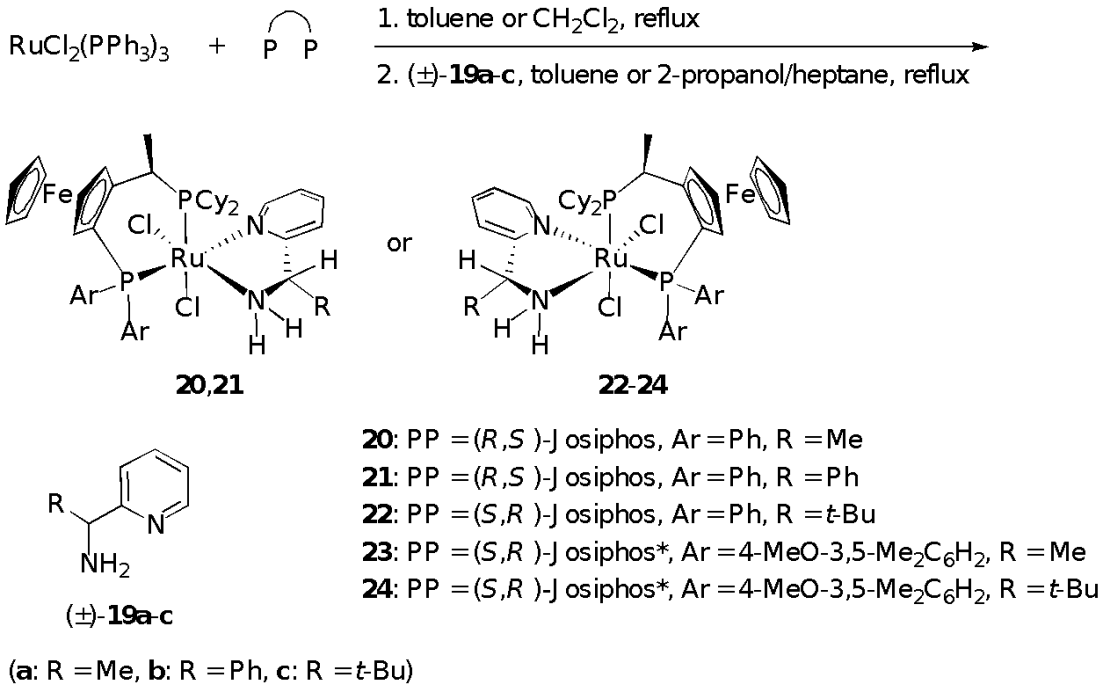
Eliminare spazio

Interstingly, we found that a single diastereomer complex *cis*-$RuCl_2$(PP)(RAmpy) can easily be obtained in high yield through a one-pot reaction of $RuCl_2(PPh_3)_3$ with chiral (*R*,*S*)-Josiphos and an excess of racemic RAmpy derivative displaying a stereogenic carbon bound to the NH_2 function [22].

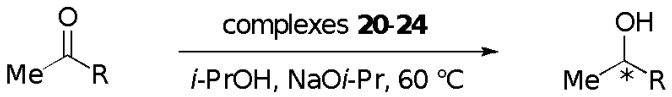
Eliminare spazio

Thus, when $RuCl_2(PPh_3)_3$ and (*R*,*S*)-Josiphos were treated with racemic 1-(pyridin-2-yl)ethanamine (**19a**) (2.5 equiv) at room temperature, a mixture of complex **20** and two $RuCl_2$[(*R*,*S*)-Josiphos][(*R*)-

19a] diastereomers were formed (Scheme 12). Importantly, upon heating at 110 °C these two isomeric complexes exchanged the (*R*)-**19a** ligand with (*S*)-**19a**, present in excess in solution, giving **20** as the sole diastereomer (55% yield). Similarly when ligands (±)-**19b**,**c** were used, complexes **21** (81%) and **22** (71%), respectively, were easily isolated as single diastereomers. Complex **21** showed the same arrangement observed for **20**, with the phenyl group bound to a carbon in *S* configuration, whereas in **22** the *t*-butyl substituent took *R* configuration (Scheme 12). The complexes *cis*-$RuCl_2$[(*S*,*R*)-Josiphos*][(*R*)-**19a**] (**23**) and *cis*-$RuCl_2$[(*S*,*R*)-Josiphos*][(*R*)-**19c**] **24** were also prepared using the bulkier (*S*,*R*)-Josiphos* in place of (*R*,*S*)-Josiphos. These complexes (0.05 mol%) and NaO*i*-Pr (2 mol%) in 2-propanol at 60 °C efficiently catalyzed the TH of ketones with both high TOF (up to 7 x 10^4 h^{-1}) and enantioselectivity (up to 99% ee) (Scheme 13). Interestingly, complexes **20**–**22** could also be generated *in situ* with the racemic ligands **19a**–**c**, showing the same enantioselectivity as the isolated complexes. Thus, for instance, *in situ* generated *cis*-$RuCl_2$[(*R*,*S*)-Josiphos][(*S*)-**19a**], prepared by heating at reflux a 2-propanol solution of $RuCl_2(PPh_3)_3$ and *(R,S)*-Josiphos (2 h) with (±)-**19a** (3 equiv) (reflux, 2 h), promoted the TH of acetophenone in basic 2-propanol at 60 °C to give in 10 min (*R*)-1-phenylethanol with both high TOF (4 x 10^4 h^{-1}) and enantiomeric excess (95%).



Scheme 12. Synthesis of the Ru-complexes **20**–**24**.



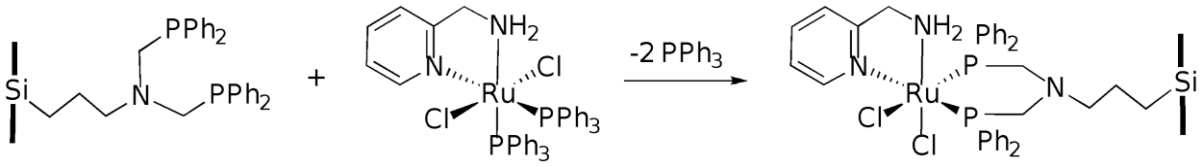
complex	R	conv (%)	t (min)	TOF (h^{-1})	ee (%)(conf)
20	Ph	97	5	6.3×10^4	96 (*R*)
20	2-MeC_6H_4	95	10	4.4×10^4	98 (*R*)
20	3-$MeOC_6H_4$	98	5	6.6×10^4	99 (*R*)
21	Ph	97	10	6.7×10^4	95 (*R*)
22	Ph	96	10	7.0×10^4	95 (*S*)
22	2-MeC_6H_4	98	40	2.6×10^4	97 (*S*)
22	2-ClC_6H_4	99	30	2.7×10^4	98 (*S*)
22	2-$MeOC_6H_4$	94	10	3.0×10^4	97 (*S*)
23	Ph	97	10	4.0×10^4	96 (*S*)
24	Ph	97	10	3.4×10^4	97 (*S*)
24	2-ClC_6H_4	99	30	2.4×10^4	97 (*S*)
24	2-$MeOC_6H_4$	98	30	2.5×10^4	98 (*S*)
24	3-$MeOC_6H_4$	97	10	2.6×10^4	>99 (*S*)

Reaction conditions: ketone (0.1 M), complex (0.05 mol%), NaO*i*-Pr (2 mol%) in *i*-PrOH at 60 °C.

Scheme 13. ATH of aromatic ketones catalyzed by the Ru-complexes **20**–**24**.

Attempts were also made to prepare heterogeneous TH catalysts based on Ampy [23]. The preparation of the model silicon containing diphosphine $(CH_3CH_2O)_3Si(CH_2)_3N(CH_2PPh_2)_2$ (ATM) was prepared in high yield by reacting (3-aminopropyl)triethoxysilane, paraformaldehyde and diphenylphosphine in toluene at 80 °C. The corresponding homogeneous complexes *cis*-$RuCl_2$(Ampy)[$RN(CH_2PPh_2)$] (R = $(CH_3CH_2O)_3Si$-$(CH_2)_3$) showed very high catalytic activity (TOF > 3 x 10^5 h^{-1}) in the TH of acetophenone in 2-propanol. Following this procedure, the diphosphine –$N(CH_2PPh_2)_2$ function was attached to the surface of three different kinds of silica by means of two alternative methods. Thus, 3-{bis-[(diphenylphosphanyl)methyl]amino}propyl-functionalized silica gel (MA-Si-60) was synthesized by reaction of 3-aminopropyl-functionalized silica gel (60 Å mean pore size) with paraformaldehyde and $PHPh_2$ in refluxing toluene, whereas MA-Si-150 and mesoporous MA-Si-MCM-41 were prepared by reaction of ATM with Davisil silica (150 Å mean pore size) and MCM-41 mesoporous silica, respectively. As depicted in Scheme 14, by reacting the –$(CH_2)_3N(CH_2PPh_2)_2$ functionalized inorganic materials and *trans*,*cis*-$RuCl_2(PPh_3)_2$(Ampy) in boiling 2-propanol, three different Ru(II)-based immobilized catalysts, namely, Ru-MA-Si-60, Ru-MA-Si-150, and Ru-MA-Si-MCM-41, were prepared. The silica-anchored complexes were tested in the TH of acetophenone, which was found to be fast and quantitative. Importantly, the effect of the nature of the silica support on the activity of the catalyst was almost negligible. It was possible to reuse the catalytic system for a second cycle without a decrease in the activity, but the efficiency of the catalyst considerably diminished in

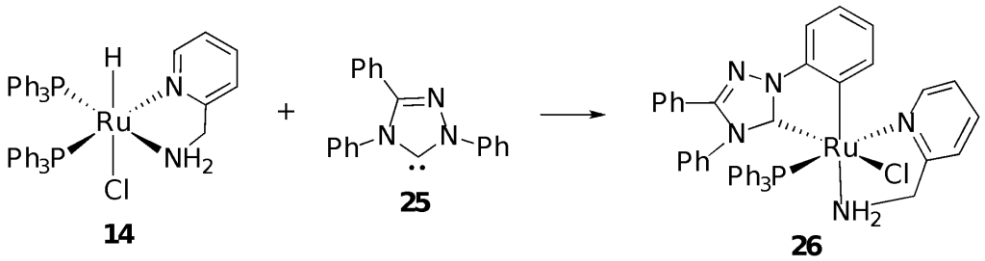
successive reuses.



Scheme 14. Synthesis of heterogeneous TH catalysts based on Ru-Ampy complexes.

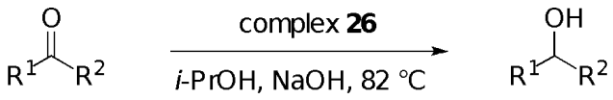
2.1.2. Carbene-Ampy ruthenium complexes

Heterocyclic carbene ligands have been successfully employed in homogeneous catalysis on account of their favorable properties, such as low oxygen and thermal sensitivity, associated to a relatively strong bonding [24]. However, for the TH of carbonyl compounds only a few Ru- catalysts based on carbene ligands have been reported [25]. With the aim to prepare catalysts that could associate the strong ligand acceleration effect of Ampy and high stability, we found that the monohydride *trans,cis*-$RuHCl(PPh_3)_2$(Ampy) (**14**) reacts straightforward with the free carbene 1,3,4-triphenyl-4,5-dihydro-1*H*-1,2,4-triazol-5-ylidene **25**, affording the orthometalated Ru-compound **26** (Scheme 14) [26].



Scheme 15. Synthesis of the Ru-complex **26**.

This complex (0.05 mol%) in the presence of NaOH in refluxing 2-propanol is an efficient TH catalyst for the reduction of numerous substrates, as alkyl aryl and dialkyl ketones, affording TOF up to 1.2×10^5 h^{-1} (Scheme 16). The comparison of the activity of the Ampy-based catalysts here reported, showed that the mixed carbene phosphine **26** is exteremely active, its rate being only inferior to that of the diphosphine complexes *cis*-$RuCl_2$(PP)(Ampy). Thus, the high activity of **26** was ascribed to the presence of the strong orthometalated carbene ligand that retards the deactivation of the catalyst, a behavior observed also for the cyclometalated phosphine complex **3 3** (Scheme 3).



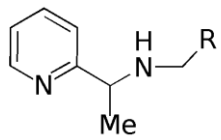
R^1	R^2	conv (%)	time (min)	TOF (h^{-1})
Ph	Me	99	5	1.2×10^5
2-ClC_6H_4	Me	90	10	5.0×10^4
3-$MeOC_6H_4$	Me	98	10	7.0×10^4
3,4-$(MeO)_2C_6H_4$	Me	98	2	1.2×10^5
n-C_5H_{11}	Me	96	10	7.0×10^4
CH_2=$CHCH_2CH_2$	Me	96	15	5.0×10^4
-$CH_2(CH_2)_3CH_2$-		99	5	1.0×10^5

Reaction conditions: ketone (0.1 M) in 2-propanol, ketone/Ru/NaOH = 2000/1/40, 82 °C.

Scheme 16. TH of ketones catalyzed by the Ru-complex **26**.

2.1.3. Tridentate NNN and NNO Ampy-based ruthenium complexes.

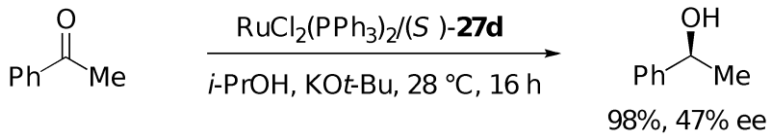
Brunner and co-workers carried out a study on the utilization of a series of bidentate NN and tridentate NNX (X = N, O) ligands based on the Ampy framework, characterized by the presence of a stereogenic center bonded to both the pyridine ring and the amine nitrogen (Fig. 3) [27]. These ligands, (*S*)- and (*R*)-**27a**–**g**, were reacted with $RuCl_2(PPh_3)_3$ and assessed as *in situ* catalysts in TH of acetophenone with isopropanol and KO*t*-Bu (acetophenone/Ru = 200:1). The secondary amine ligand (*S*)-**27d** gave the best results with almost quantitative conversion and 47% ee (Scheme 17*)*.



(*R*)- and (*S*)-**27a-g**

a: R = 2-pyridyl; **b**: R = 2-quinolinyl
c: R = 2-hydroxyphenyl; **d**: R = 3,5-di-*tert*-butyl-2-hydroxyphenyl
e: R = isopropyl; **f**: R = phenyl; **g**: R = 2-naphthyl

Fig. 3. Chemical structure of the ligands (*S*)- and (*R*)-**27a**–**g**.



Scheme 17. ATH of acethophenone catalyzed by the Ru-complex **27d**.

Next, the same group synthesized the bidentate and tridentate aminopyridine ligands **28**–**30** (Fig. 4), which were assessed in TH of acetophenone with 2-propanol (Scheme 18) [28,29]. High enantioslectivity was observed with the system $RuCl_2(PPh_3)_3$/(*S*)-**28**, affording quantitative formation of (*S*)-1-phenylethanol (94% yield) with 96.7% ee. Several Ru-complexes ($RuCl_2(PPh_3)_3$, $RuCl_2(DMSO)_4$, Ru_2Cl_4((*R*,*R*)-DIOP)$_2$ and [$RuCl_2$(*p*-cymene)]$_2$ in combination with ligand (*S*)-**28** were also tested as precatalysts. Among them, $RuCl_2(PPh_3)_3$ was the best one because its PPh_3 ligands could be easily replaced by (*S*)-**28** unlike what happens with the ligands in the other complexes. Moreover, when the TH was carried out by addition of 3 or 10 equivalents of additional PPh_3 to $RuCl_2(PPh_3)_3$/(*S*)-**28**, a decreasing of the catalytic activity and enantioselectivity was observed, indicating that the amount of PPh_3 is not only contributing to the activity of the catalyst, but also plays a role in the chirality transfer. The introduction of a further sterogenic center into the binaphthyl ligand obtained by preparing diastereomeric ligands **30** and **31**, whose absolute configuration was not determined, did not improve the enantioselectivity of the parent ligand (*S*)-**28**. PPh_3 removing reagents such as CuCl, 2,2,6,6-tetramethylpiperidin-1-oxyl or trimethylamineoxide improved the catalytic performance to enantioselectivities up to 98.5% ee. The failure of (*S*)-**29** demonstrated that the phenolic OH function is crucial for the catalytic activity and enantioselectivity.

These findings led to a mechanistic proposal including dissociation equilibria of PPh_3 and chelate ring opening of the tridentate chiral binaphthyl ligand (Scheme 19). The precatalyst $RuCl_2(PPh_3)_3$ contains three phosphine ligands, while the experimentally determined optimum quantity lies in the range of one or two equivalents. Taking into account that the chiral binaphthyl ligand may bind in a bidentate or tridentate way and that two further coordination sites are needed for binding the substrates, a dissociation of PPh_3 from $RuCl_2(PPh_3)_3$ must occur in order to enable the complex to enter the catalytic cycle (first step in Scheme 19). S in Scheme 19 may stand for a hydride or a hydrogen donor, such as 2-propanol, resulting in a neutral species in the first case or a cationic species in the latter case. The position of the open site ( ) is chosen arbitrarily as well as the arrangement of the various ligands around the metal center, while chelate ring opening of the chiral tridentate ligand may occur at the pyridine or at the phenolate side. The horizontal branch of Scheme 19 shows how an open site is formed by dissociation of PPh_3. The substrate can subsequently bind to the metal center, reacting rapidly with high enantiomeric excess. In the perpendicular branch an open site is generated by chelate ring opening, the consequence of which is a change in the chiral environment of the metal center lowering the enantiomeric excess in a slower reaction.

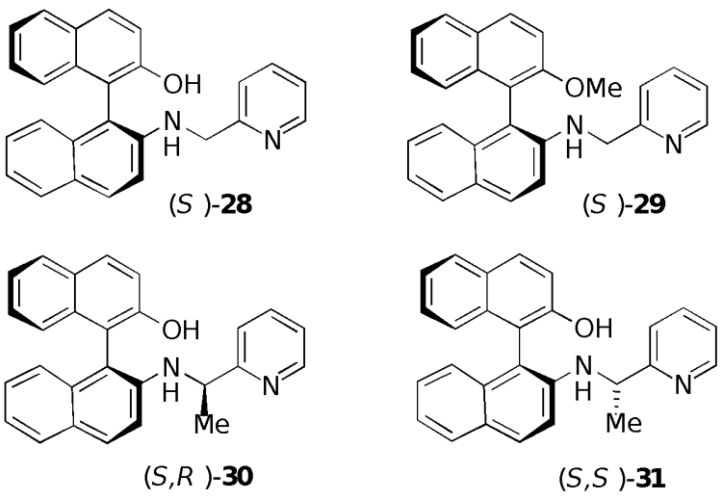
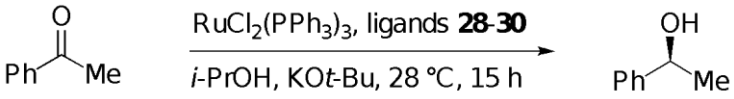


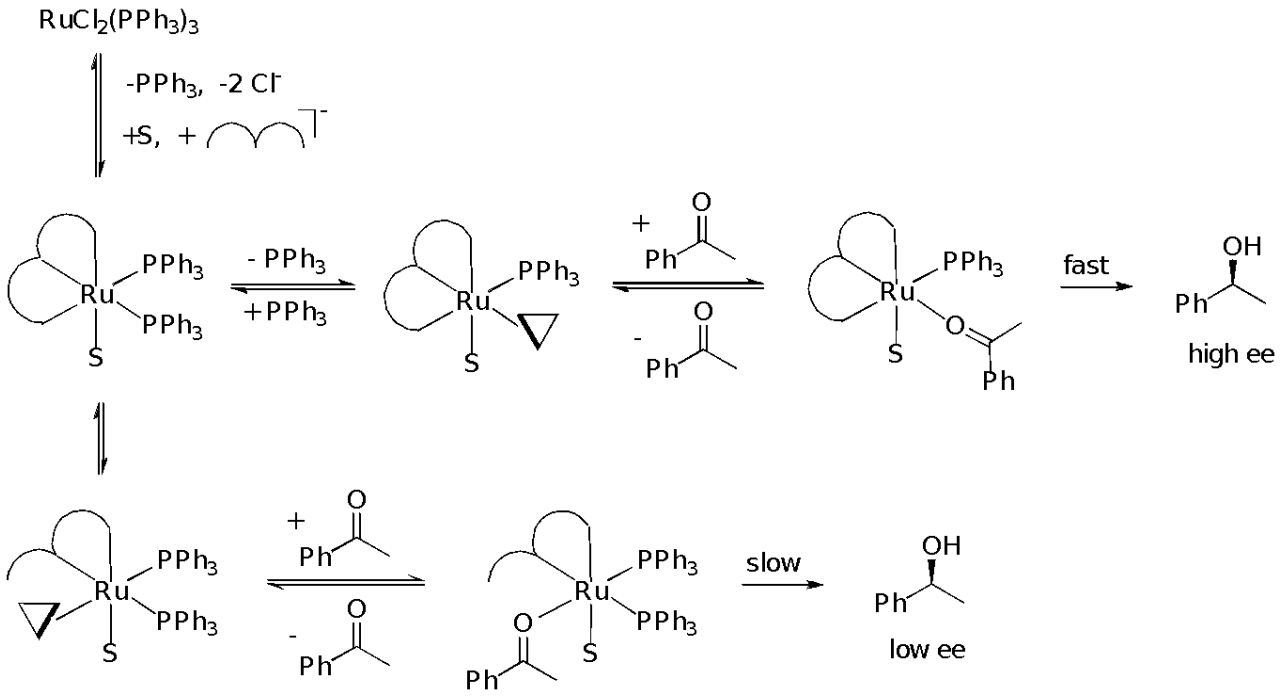
Fig. 4. Chemical structures of *N,N*-bidentate ligands based on 2-amino-1,1-binaphthyl-2-ol and pyridine moieties.



ligand	yield (%)	ee (%)
(*S*)-**28**	86	96.3[a]
(*S*)-**28**	94	96.7[b]
(*S*)-**29**	38	2.6[a]
(+)-**30**	93	92.8[a]
(-)-**30**	83	85.9[a]
(*S*)-**28**	59	98.5[a,c]

[a]Ratio $RuCl_2(PPh_3)_3$/ligand/ KO*t*-Bu/PhCOMe = 1/1.1/2.1/200
[b]Ratio $RuCl_2(PPh_3)_3$/ligand/ KO*t*-Bu/PhCOMe = 1/1.1/3.2/100
[c]CuCl (30 equiv) was added

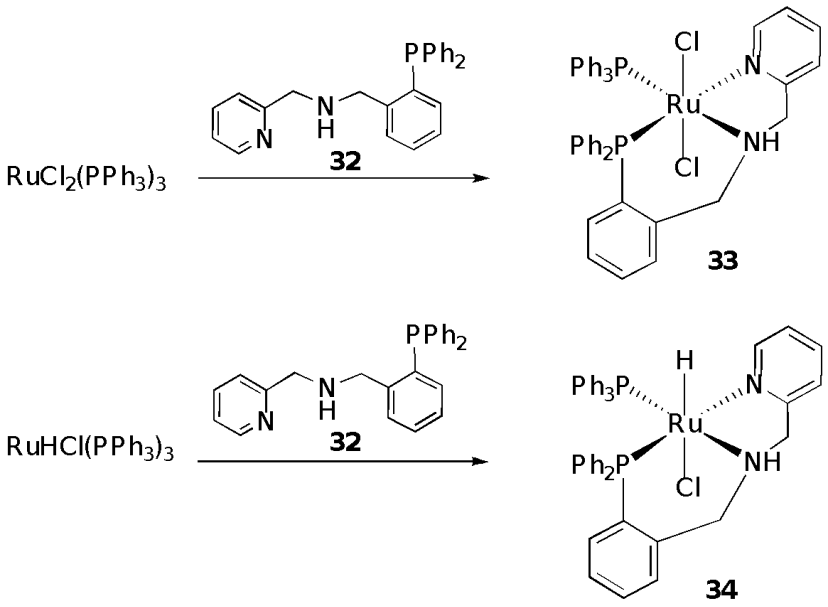
Scheme 18. ATH of acetophenone catalyzed by $RuCl_2(PPh_3)$/**28**–**30**.



Scheme 19. Proposed mechanism, including dissociation equilibria of PPh_3 and chelate ring opening of the tridentate chiral binaphthyl ligand in TH of acetophenone with 2-propanol catalyzed by $RuCl_2(PPh_3)_3$ and ligands **28**–**30**.

2.1.4. Tridentate PNP Ampy-based ruthenium complexes.

We were also interested in Ru-complexes containg tridentate ligands based on Ampy. Thus, the complex t*rans*-$RuCl_2(PPh_3)$(PNN) **33** was easily obtained by reaction of $RuCl_2(PPh_3)_3$ with the PNN ligand **32**, prepared from Ampy and 2-(diphenylphosphino)benzaldehyde (Scheme 20) [30]. The reaction between equimolar amounts of $RuHCl(PPh_3)_3$ and **32** in refluxing heptane and then CH_2Cl_2 afforded the hydride complex **34** (Scheme 20).



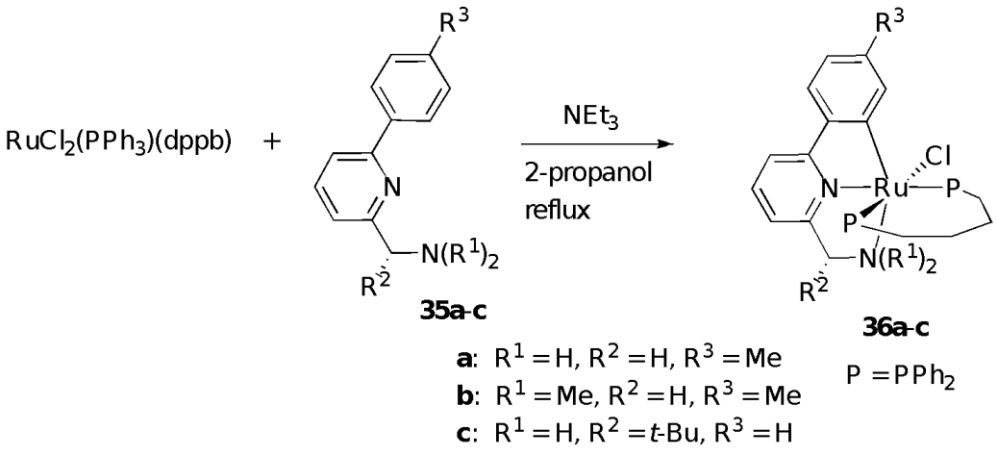
Scheme 20. Synthesis of the Ru-complexes **33** and **34**.

Complex **33** was found to catalyze the quantitative reduction in 2 min of acetophenone to 1-phenylethanol in refluxing 2-propanol containing NaO*i*-Pr (acetophenone/complex/NaO*i*-Pr = 1000:1:40), affording TOF = 1.9×10^5 h^{-1} at 50% conversion, which is a value of the same order to that reported for the related complexes *cis*,*cis*-$RuCl_2$(diphosphine)(Ampy) [17]. On the other hand, the activity of the monohydride complex **34** was lower (TOF up to 1.6×10^4 h^{-1}) compared to that of the dichloride precursor **33**. In absence of base, complex **34** did not catalyze the reduction of acetophenone suggesting that dihydride Ru-species are involved in the catalysis. By using PNN ligands with a CH_2CH_2 backbone connected to the pyridine ring, instead of one CH_2 spacer, the resulting complexes showed a remarkably lower activity, indicating that the presence of a five-membered chelate ring involving the pyridine is crucial to achieve high performance in TH.

2.1.5. Tridentate CNN Ampy-based ruthenium complexes

With the aim to obtain both fast and robust catalytic systems, we designed Ru-complexes in which a diphosphine ligand is combined with a cyclometalated framework containing the Ampy motif. In this context, it is well known that CN orthometalated pyridine Ru-complexes can easily be prepared from 2-phenylpyridine and 6-phenyl-2,2'-bipyridine [31].

Initially, the Ru-complexes of formula RuCl(CNN)(dppb) **36a**–**c** (Scheme 21) were prepared by treating the Ru-precursor $RuCl_2(PPh_3)$(dppb) with an equimolar amount of the 2-aminomethyl-6-arylpyridines **35a**–**c** in 2-propanol and in the presence of NEt_3 at reflux temperature (Scheme 21) [32]. Ligand **35c** was obtained by distereoselective reduction of an enantiopure *N*-*p*-toluenesulfinyl ketimine derived from the related 2-pyridyl ketone, followed by hydrolysis [33]

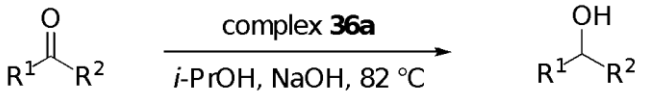


Scheme 21. Synthesis of the Ru-complexes **36a**–**c**.

Complex **36a** displayed an exceptionally high catalytic activity in TH of ketones with 2-propanol in

the presence of NaOH. As shown in Scheme 22, alkyl- aryl, dialkyl and diaryl ketones were quantitatively and chemoselectively (a terminal olefinic bond was preserved) reduced to the related alcohols in few minutes, using a low amount of **36a** (0.005 mol%) and with TOF up to 2.5×10^6 h^{-1}, which are the highest values reported in the literature . The analogue of **36b** with the NMe_2 instead of NH_2 moiety showed a poor activity, indicating that fast catalytic TH is assisted by the NH_2 functionality.

Importantly, with 0.001 mol% of **36a**, complete reduction of acetophenone was achieved in 1 h, and experiments carried out at 5 x 10^{-4} mol% of the complex afforded a TON = 1.7×10^5. As example of application of this protocol, 1.97 g of 4-chlorobenzydrol was obtained in 90% yield from 4-chlorobenzophenone in 2 h by using 0.076 mg of **36a** (0.001 mol%).

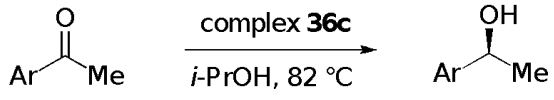


R^1	R^2	conv (%)	time (min)	TOF (h^{-1})
Ph	Me	98	5	1.1×10^4
3-$MeOC_6H_4$	Me	98	2	1.9×10^6
3-ClC_6H_4	Me	99	1	2.5×10^6
n-C_5H_{11}	Me	99	10	5.0×10^5
CH_2=$CH(CH_3)CH_2CH_2$	Me	97	5	7.0×10^5
-$CH_2(CH_2)_2CH_2$-		99	5	1.2×10^6
-$CH_2(CH_2)_3CH_2$-		99	2	1.5×10^6
4-ClC_6H_4	Ph	98	10	5.3×10^5

Reaction conditions: ketones (0.1 M), complex (0.005 mol%) and NaOH (2 mol%) in 2-propanol at 82 °C.

Scheme 22. TH of ketones catalyzed by the complex **36a**.

When the chiral complex **36c** was used, fast reduction of different methyl-aryl ketones was observed under the same reaction conditions employed for **36a** (Scheme 23). The reduction rates were comparable to those of **36a**, leading to the related alcohols in a few minutes (TOF = 5.4 x 10^5 to 1.4 x 10^6 h^{-1}) and with good enantiomeric excesses in the range 70–88%, the best result being obtained with 2-methoxyacetophenone. Furthermore, the same catalytic performance could be obtained generating the catalyst *in situ*, by reaction of $RuCl_2(PPh_3)$(dppb) with the ligand **35c** (2 equiv) in 2-propanol at reflux, showing that the formation of **36c** is quite straightforward.

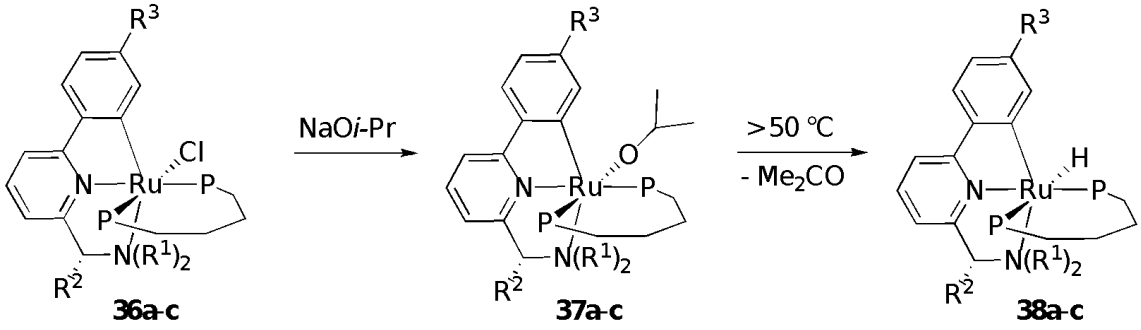


Ar	conv (%)	time (min)	TOF (h^{-1})[a]	ee (%)
Ph	98	5	9.3×10^5	71
2-ClC_6H_4	99	5	6.8×10^5	70
2-$MeOC_6H_4$	96	5	5.4×10^5	88
3-$MeOC_6H_4$	97	2	1.4×10^6	71
Ph	98	10	6.6×10^5	72[b]
2-ClC_6H_4	95	5	6.8×10^5	70[b]
2-$MeOC_6H_4$	92	5	6.0×10^5	88[b]

Reaction conditions: ketone 0.1 M in 2-propanol, ketone/Ru/NaO*i*-Pr = 20000/1/400 at 82 °C. [a]Turnover frequency at 50%. [b]Complex **36c** was prepared *in situ* by treatment of $RuCl_2(PPh_3)$(dppb) with the ligand **35c** (1:2 molar ratio) in 2-propanol at reflux for 10 min.

Scheme 23. ATH of aryl-methyl ketones catalyzed by the complex **36c**.

When the complexes **36a**–**c** were treated with NaO*i*-Pr in 2-propanol-toluene at room temperature the intermediate alkoxides **37a**–**c** were obtained. By heating this solution above 50 °C the hydride complexes **38a**–**c** were formed through elimination of acetone on evaporation of the medium (Scheme 24). The hydride **38a** (0.01mol%) is a catalyst of impressive activity in refluxing 2-propanol leading to complete conversion of acetophenone in a few minutes with TOF ranging from 4.8×10^4 h^{-1} (in the absence of base) to 8.0×10^5 h^{-1} (in the presence of a ten fold excess of NaO*i*-Pr).

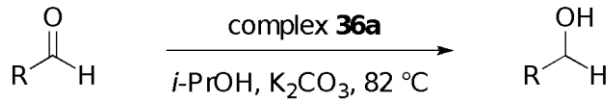


P = PPh_2
a: R^1 = H, R^2 = H, R^3 = Me; **b**: R^1 = Me, R^2 = H, R^3 = Me; **c**: R^1 = H, R^2 = *t*-Bu, R^3 = H

Scheme 24. Synthesis of the Ru-hydride complexes **38a**–**c**.

Complex **36a** also catalyzed the fast TH of aliphatic, aromatic and unsaturated aldehydes to primary alcohols with 2-propanol in the presence of the weak base K_2CO_3 (Scheme 25) [34]. The very short

reaction time obtained by this catalyst limits side reactions such as aldol condensation and catalyst deactivation via decarbonylation, affording in this way the chemoselective aldehyde TH. Thus, *trans*-cinnamaldehyde was quickly and quantitatively converted into cinnamyl alcohol in 30s, while further reduction of the C=C double bond required hours.



R	conv (%)	time (sec)	TOF (h^{-1})
Ph	99	30	3.0×10^5
4-MeC_6H_4	99	2 min	8.0×10^4
2,4-$Me_2C_6H_3$	98	20	4.5×10^5
$C_2H_5CH(CH_3)$	99	30	2.4×10^5
n-C_5H_{11}	99	30	3.0×10^5
c-C_6H_{11}	99	5 min	2.0×10^5
$PhCH(CH_3)$	99	2 min	9.0×10^4
(*E*)-PhCH=CH	99	30	3.3×10^5
$CH_3CH=C(CH_3)$	99	30	2.5×10^5

Reaction conditions: aldehyde (0.1 M), complex (0.05 mol %) and K_2CO_3 (5 mol%) in 2-propanol at 82 °C.

Scheme 25. TH of aldehydes catalyzed by the Ru-complex **36a**.

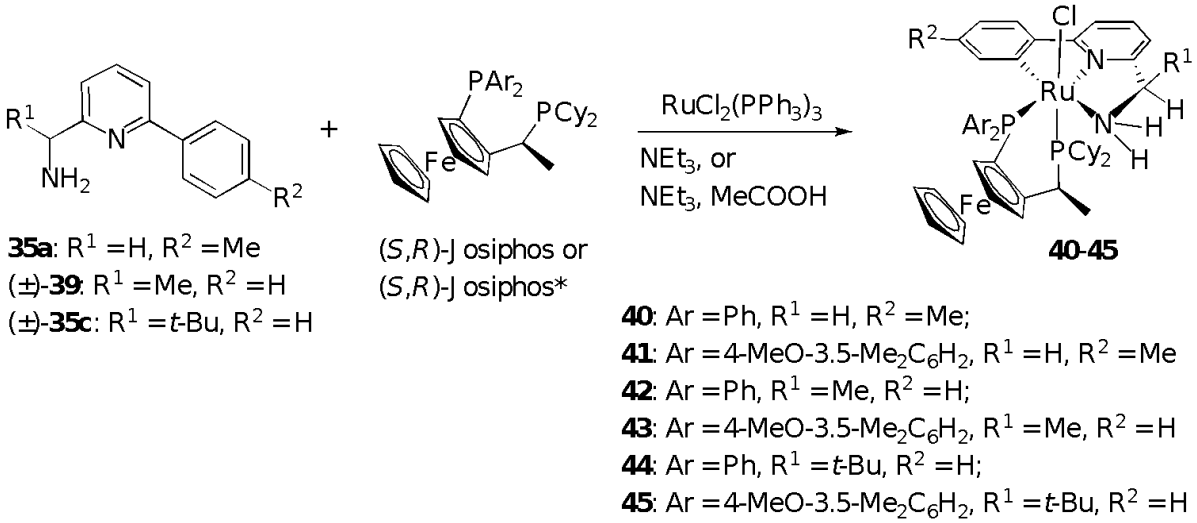
We later reported a straightforward approach for the preparation of highly enantioselective catalysts containing both chiral phosphine and pincer ligands, obtained without the need to use the optically active pincer ligand [35].

Initially, the thermally stable ortho-metalated chiral derivative **40** was easily prepared by treatment of $RuCl_2(PPh_3)_3$ with 1.2 equiv of (*S*,*R*)-Josiphos in refluxing toluene, followed by reaction with (4-methylphenyl-2-yl)methanamine **35a** (1.3 equiv) and NEt_3 in refluxing 2-propanol (Scheme 26). Similarly to **40**, the complex **41** was obtained with the bulkier (*S*,*R*)-Josiphos*.

Treatment of $RuCl_2(PPh_3)_3$ with (*S*,*R*)-Josiphos and racemic 1-(6-phenylpyridin-2-yl)ethanamine **39** resulted in the formation of two Ru-diastereoisomers in about 1:1 ratio (Scheme 26). Interestingly, by performing the reaction with an excess of (±)-**39** (4 equiv) in the presence of NEt_3 and 0.5 equiv of AcOH, the complex **42** was formed in 70% yield predominantly as one stereoisomer (>92% major isomer). Under these reaction conditions, the combination of (*S*,*R*)-Josiphos* and (±)-**39** led to the species **43** (>93% major isomer) in 63% yield. The weak acid proved to facilitate the formation of the thermodynamically most stable diastereoisomer, possibly through protonation and decoordination of the ortho-metalated CNN ligand of the kinetic product. Control experiments showed that reaction of the $RuCl_2(PPh_3)_3$/(*S*,*R*)-Josiphos or (*S*,*R*)-Josiphos* system with enantiopure (*R*)-**39** led to **42** and **43**

as single stereoisomers, namely, the major isomers obtained in the synthesis of **42** and **43** from (±)-**39**. In addition, the use of (±)-**39** or (*R*)-**39** led to complexes that display the same catalytic activity. Finally, derivatives **44** and **45** were isolated as single isomers (65 and 67% yields) from $RuCl_2(PPh_3)_3$, (*S,R*)-Josiphos or (*S,R*)-Josiphos*, and (±)-**36c** in the presence of AcOH. In these cases, the higher steric hindrance exerted by the *t*-Bu group of **35c** relative to the Me group of **39** resulted in an increased diastereoselectivity.

Pincer complexes **40**–**45** are ~~s~~remarkably active catalysts for the reduction of alkyl aryl ketones in basic alcohol media by TH, achieving enantioselectivities of up to 99% ee (Scheme 27). In 2-propanol and with NaO*i*-Pr (2 mol%) at 60 °C, TH of a variety of ketones was accomplished with high TOF (10^5–10^6 h^{-1})) by a catalyst loading as low as 0.002 mol%. These are the most productive catalysts for asymmetric TH reported to date and show a high potential for applications. Thus, (S)-1-(3-trifluoromethylphenyl)ethanol, which is a building block for the synthesis of the agricultural fungicide (*S*)-MA20565, was isolated in 90% yield with 95% ee (4.10 g) by reduction of the corresponding ketone using 0.5 mg of complex **43** (0.002 mol%).

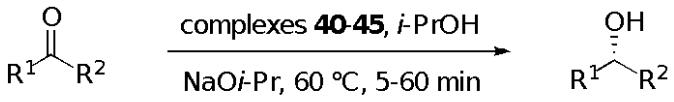


35a: R^1 = H, R^2 = Me
(±)-**39**: R^1 = Me, R^2 = H
(±)-**35c**: R^1 = *t*-Bu, R^2 = H

(*S*,*R*)-Josiphos or
(*S*,*R*)-Josiphos*

40: Ar = Ph, R^1 = H, R^2 = Me;
41: Ar = 4-MeO-3.5-$Me_2C_6H_2$, R^1 = H, R^2 = Me
42: Ar = Ph, R^1 = Me, R^2 = H;
43: Ar = 4-MeO-3.5-$Me_2C_6H_2$, R^1 = Me, R^2 = H
44: Ar = Ph, R^1 = *t*-Bu, R^2 = H;
45: Ar = 4-MeO-3.5-$Me_2C_6H_2$, R^1 = *t*-Bu, R^2 = H

Scheme 26. Synthesis of the Ru-complexes **40**–**45**.

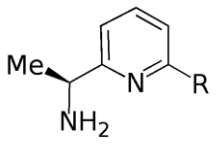


complex	R^1	R^2	conv (%)	time (min)	TOF (h^{-1})	ee (%)
40	Me	Ph	97	30	1.3×10^5	70
41	Me	Ph	94	30	1.0×10^5	92
42	Me	Ph	98	30	1.6×10^5	81
43	Me	Ph	98	10	1.8×10^5	95
43	Me	4-ClC_6H_4	97	10	$1,5 \times 10^5$	96
43	Me	3-$MeOC_6H_4$	97	30	1.4×10^5	97
43	Me	3,5-$(MeO)_2C_6H_3$	97	10	1.8×10^5	98
43	Me	2-pyridyl	99	30	1.2×10^5	93
43	Me	3-$F_3CC_6H_4$	98	30	1.6×10^5	95
43	Me	2-naphthyl	97	5	2.0×10^5	97[a]
43	Me	1-naphthyl	98	60	5.5×10^4	98[a]
43	Et	Ph	98	60	1.1×10^4	99
44	Me	Ph	95	30	1.1×10^5	85
45	Me	Ph	96	30	9.0×10^4	95
45	Me	3-MeC_6H_4	96	30	1.3×10^5	92
45	Me	2-ClC_6H_4	92	60	7.0×10^4	91
45	Me	3,5-$(MeO)_2C_6H_3$	95	10	1.6×10^5	97

Reaction onditions: ketone (0.1 M), complex (0.005 mol%) and NaO*i*-Pr (2 mol%) in *i*-PrOH at 60 °C. [a]Complex 0.01 mol%.

Scheme 27. ATH of aromatic ketones catalyzed by the Ru-complexes **40**–**45**.

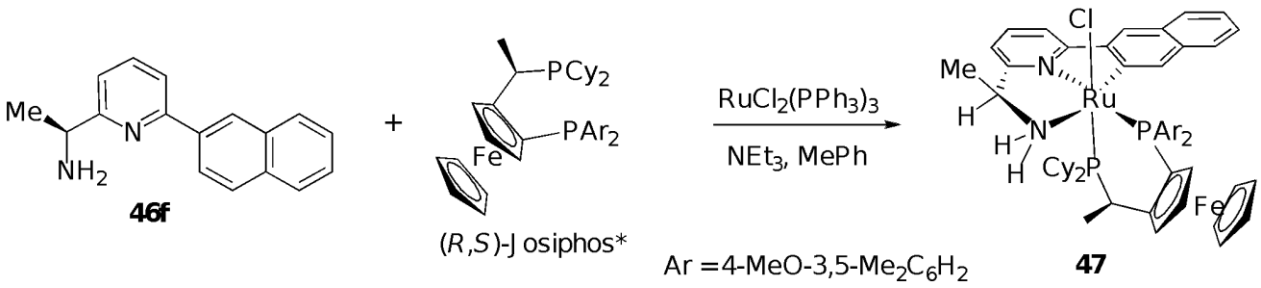
The series of chiral HCNN ligands, (*S*)-**39** and (*S*)-**46a**–**f**, has been recently prepared from (*R*)-1-(6-bromopyridin-2-yl)ethanol obtained by a chemoenzymatic procedure (Fig. 5**)** [36]. The *in situ* generated pincer complexes RuCl(CNN)(PP), prepared from $RuCl_2(PPh_3)_3$, (*R*,*S*)-Josiphos* and these ligands efficiently catalyzed the TH of acetophenone in 2-propanol at 60 °C and in the presence of NaO*i*-Pr. The best ligand resulted to be the 2-naphthyl ligand (*S*)-**46f** that afforded (*R*)-1-phenylethanol in 98% conversion with 92% ee and TOF = 10^5 h^{-1}. On the basis of these data, the complex **47** was prepared from (*R*,*S*)-Josiphos* in combination with (*S*)-**46f** (Scheme 28). Complex **47** (0.005 mol%) displaying the correctly matched chiral PP and CNN-ligands, was highly active and productive catalyst for TH of alkyl (hetero)aryl ketones (TOF = 10^5-10^6 h^{-1} with up to 99% ee) (Scheme 29).



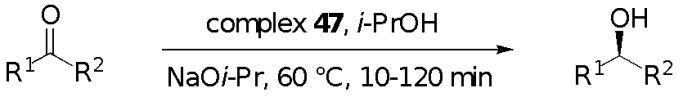
39, **46a-f**

39: R = Ph; **46a**: R = 4-$MeOC_6H_4$
46b: R = 4-$F_3CC_6H_4$; **46c**: R = 3,5-$Me_2C_6H_4$
46d: R = 3,5-$(F_3C)_2C_6H_4$
46e: R = 1-naphthyl; **46f**: R = 2-naphthyl

Fig. 5. Chemical structure of the ligands **39** and **46a**–**f**.



Scheme 28. Synthesis of the Ru-complex **47** [35].



R^1	R^2	conv. (%)	time (min)	TOF (h^{-1})	ee (%)
Me	Ph	95	30	1.2×10^5	92
Et	Ph	90	120	7.7×10^4	99
Me	1-naphthyl	98	30	4.7×10^4	96
Me	2-naphthyl	96	30	1.6×10^5	93
Me	2-MeC_6H_4	80	60	2.5×10^4	96
Me	3-ClC_6H_4	99	30	1.3×10^5	99
Me	3-$F_3CC_6H_4$	99	30	2.6×10^5	96
Me	3-$MeOC_6H$	96	60	9.0×10^4	94
Me	3,5-$(MeO)_2C_6H_3$	97	30	2.1×10^5	95
Me	3,5-$(F_3C)_2C_6H_3$	99	60	1.9×10^4	98
Me	2-pyridyl	93	60	3.9×10^4	86
Me	3-pyridyl	99	30	6.6×10^4	92
Me	4-pyridyl	99	10	1.2×10^5	97

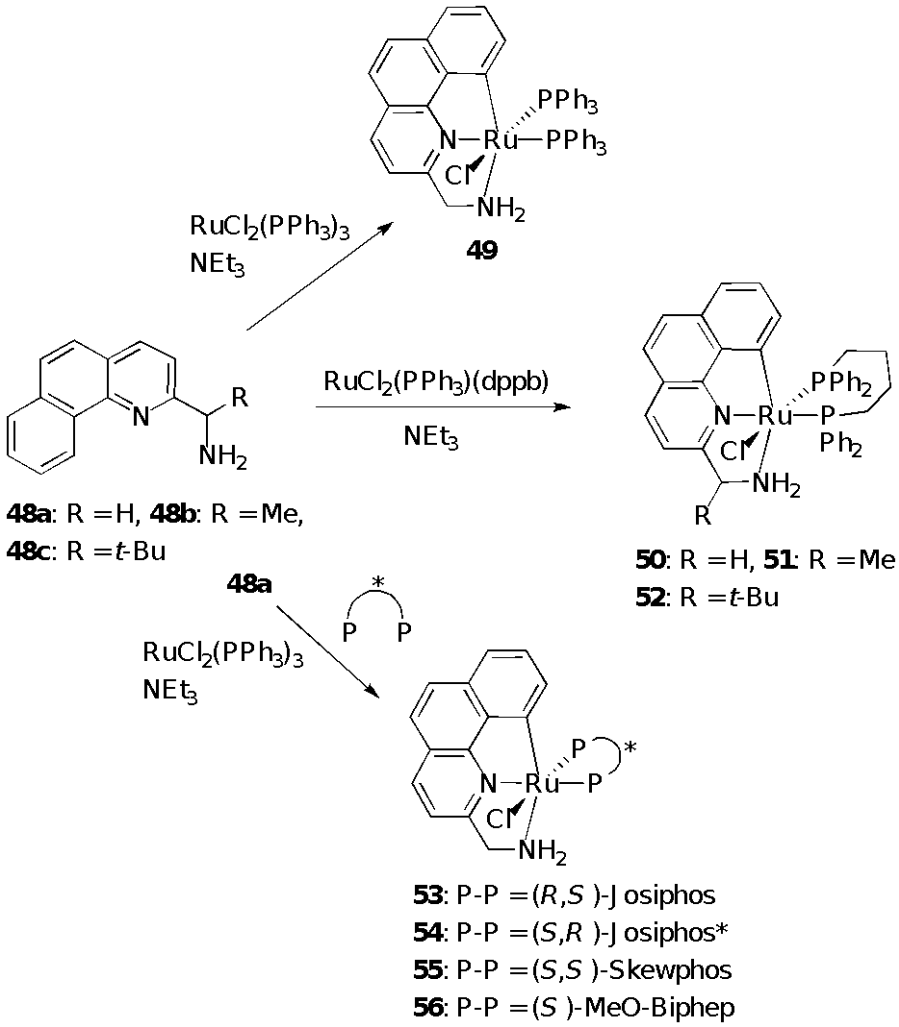
Reaction conditions: ketone (0.1 M),complex (0.005 mol%), NaO*i*-Pr (2 mol%) in *i*-PrOH, 60 °C

Scheme 29. ATH of aromatic ketones catalyzed by the Ru-complex **47**.

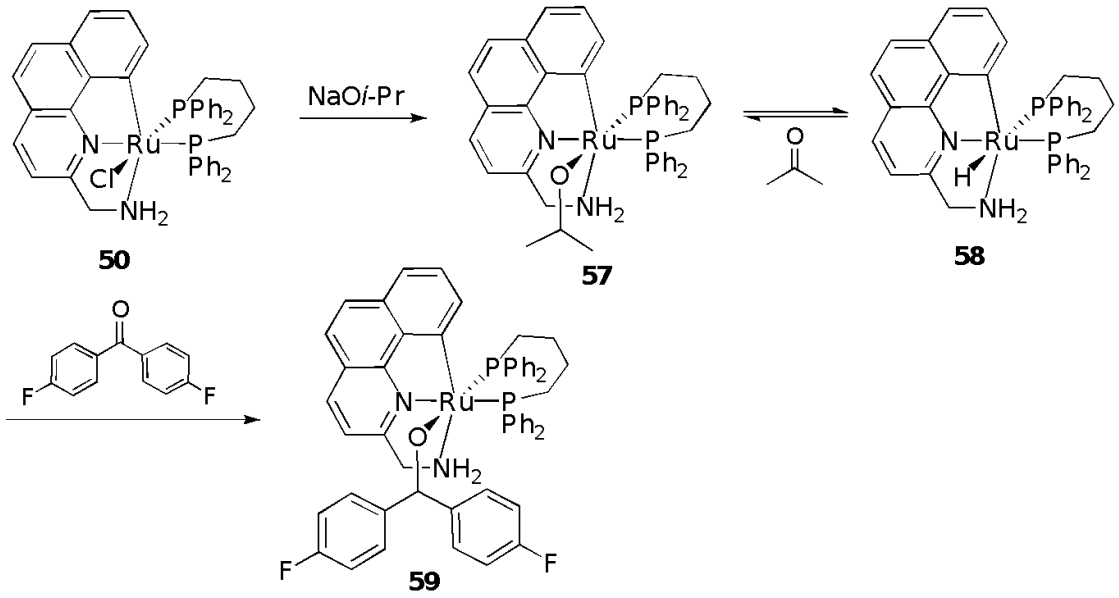
Other cyclometalated Ru-complexes containing pincer CNN ligands based on the benzo[h]qunoline framework for TH catalysis were next described by us (Schemes 30) [37]. For these CNN ligands a higher conformational rigidity is expected, compared to those based on 2-phenylpyridine, due to the presence of the planar benzo[h]quinoline system.

The reaction of 2-aminomethylbenzo[h]qunoline (**48a**) with $RuCl_2(PPh_3)_3$ in 2-propanol at reflux afforded the tridentate CNN complex **49** in 74% yield (Scheme 30), while complexes **50**–**52** were obtained from $RuCl_2(PPh_3)$(dppb) with ligand **48a** and 2-aminomethylbenzo[h]qunoline derivatives **48b** and **48c** incorporating a stereochemical center on the benzylic carbon of the CHR-NH_2 arm (R = Me, *t*-Bu) (Scheme 30). The employment of (*R*,*S*)-Josiphos, (*S*,*R*)-Josiphos*, (*S*,*S*)-Skewphos, and (*S*)-MeO-Biphep in combination with $RuCl_2(PPh_3)_3$ and ligand **48a** in refluxing toluene gave the chiral derivatives **53**–**56** (Scheme 30).

Treatment of **50** with NaO*i*-Pr (1.1 equiv) in 2-propanol/toluene mixture at 40 °C afforded a dark red solution containing the intermediate alkoxide **57**, which by evaporation of the solvent led to the hydride complex **58** through a reversible elimination of acetone (Scheme 31). A better conversion into the hydride **58** (83% yield) was achieved by stirring the alkoxide solution under H_2 for 1 h followed by evaporation of the solvent. Finally, the fluoro-substituted alkoxide **59** was easily prepared by reaction of the *in situ* formed **57** with bis(4-fluorophenyl)methanone in a 2-propanol/toluene mixture at room temperature (75% yield), through the hydride **58** (Scheme 31).

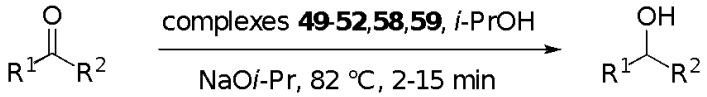


Scheme 30. Synthesis of Ru-complexes **49**–**56**.



Scheme 31. Synthesis of the Ru-complexes **57**–**59**.

Complexes **49**–**52**, **58** and **59** were efficient catalysts for TH of carbonyl compounds with 2-propanol in the presence of NaO*i*-Pr (2 mol%) (Scheme 32). TOF up to 1.8 x 10^6 h^{-1} were achieved by using 0.005 mol% of the catalyst. Much the same activity was observed for the Ru-Cl, -H, -OR (**50**, **58**, **59**) derivatives.

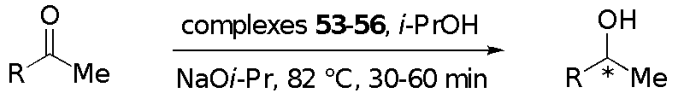


complex	R^1	R^2	conv (%)	time (min)	TOF (h^{-1})
49[a]	Me	Ph	94	15	7.0 x 10^4
50	Me	Ph	97	2	1.2 x 10^6
50	Me	2-ClC_6H_4	99	2	1.8 x 10^6
50	Me	3-$MeOC_6H_4$	97	2	1.8 x 10^6
50	Me	$CH_2CH_2CH{=}CH_2$	99	5	1.1 x 10^6
50	-$CH_2(CH_2)_3CH_2$-		97	2	1.2 x 10^6
50[b]	H	*c*-C_6H_{11}	99	5	2.0 x 10^5
51	Me	Ph	98	5	8.3 x 10^5
52	Me	Ph	98	5	1.1 x 10^6
58	Me	Ph	97	2	1.3 x 10^6
59	Me	Ph	98	2	1.4 x 10^6

Reaction onditions: ketone (0.1 M), complex (0.005 mol%), NaO*i*-Pr (2 mol%) in *i*-PrOH at 82 °C. [a]Complex = 0.02 mol%. [b]Complex = 0.01 mol%.

Scheme 32. TH of aromatic ketones catalyzed by the Ru-complexes **49**-**52**,**58** and **59**.

The chiral complex **53-56** catalyze the asymme t ric reduction of several methyl-aryl ketones with up to 97% ee and high rate (TOF = 1.9 x 10^5 h^{-1}), the derivatves **53** and **54** containg the Josiphos diphosphine displaying higher enantioselectivity with respect to **55** and **56** (Scheme 33). The *in situ* generated catalyst **54**, obtained by refluxing a 2-propanol solution of $RuCl_2(PPh_3)_3$ with (*S*,*R*)-Josiphos* (1 h) and racemic **48b** (1 h), promoted the reduction of acetophenone to (*S*)-1-phenylethanol with high rate (TOF = 1.2 x 10^5 h^{-1}) and 90% ee at 0.005 mol% catalyst loading (Scheme 33) [37]. By using the analogue *t*-Bu ligand **48c** the S alcohol was formed with 93% ee, while the substrates 1-(2-chlorophenyl)ethanone and 1-(2-methoxyphenyl)ethanone were converted to *S* alcohols with 98 and 97% ee, respectively (TOF up to 1.1 x 10^5 h^{-1}). It should be pointed out that the *in situ* generated species displayed much the same rate as the related isolated complexes RuCl(CNN)(P_2) and high enantioselectivity could be achieved through the combination of alkyl-substituted benzo[h]quinolines with bulky Josiphos ligands.



complex	R	conv. (%)	time (min)	TOF (h^{-1})	ee (%)	config
53	Ph	97	30	1.3 x 10^5	86	*R*
53	2-MeOlC_6H_4	87	60	6.0 x 10^4	89	*R*
54	Ph	98	40	1.0 x 10^5	96	*S*
54	2-MeC_6H_4	96	60	6.0 x 10^4	94	*S*
54	2-ClC_6H_4	98	40	1.2 x 10^5	97	*S*
55	Ph	95	30	1.1 x 10^5	73	*S*
56	Ph	97	30	1.9 x 10^5	26	*R*
in situ[a]	Ph	98	30	1.2 x 10^5	90	*S*
in situ[b]	Ph	98	30	1.2 x 10^5	93	*S*
in situ[b]	2-ClC_6H_4	99	30	1.1 x 10^5	98	*S*
in situ[b]	2-$MeOC_6H$	95	30	1.0 x 10^5	97	*S*

Reaction conditions: ketone (0.1 M), complex (0.005 mol%), NaO*i*-Pr (2 mol%) in *i*-PrOH at 82 °C. [a]Catalyst prepared *in situ*: $RuCl_2(PPh_3)_3$/(*S*,*R*)-Josiphos*/**48b** = 1:1.5:3. [b]Catalyst prepared *in situ*: $RuCl_2(PPh_3)_3$/(*S*,*R*)-Josiphos*/**48c** = 1:1.5:3

Scheme 33. ATH of aromatic ketones catalyzed by the Ru-complexes **51-56**.

We were interested to study pincer Ru-complexes displaying both the NH_2 functionality and an oxygen donor ligand in a *cis*-arrangement [38]. Thus, the pincer complexes **61**–**66**, showing carboxylate, phenoxide, alkoxide, silanolate and triflate ligands, were prepared in high yield starting from **36a** via substitution of the chloride with sodium or thallium compounds, or protonation of the alkoxide **60** (Scheme 34). In the solid state the formate **61** showed intermolecular NH⊕⊕⊕⊕O hydrogen bonds,

whereas the acetate **62** displayed an intramolecular interaction, as inferred from X-ray studies. Addition of phenol and alcohol compounds to the phenoxide and alkoxide complexes led to fast ligand exchange through hydrogen bond interactions.

Pincer complexes RuX(CNN)(dppb) (X = phenoxide, alkoxide) containing the Ru-NMe_2 moiety were also obtained from the Ru-complex **36b**. Treatment of **36b** with KO*i*-Pr or KO*t*-Bu, afforded the related complexes **37b** or **67**, respectively; while reaction of **37b** with 4-fluoro-3-methylphenol gave the complex **68** (Scheme 35). NMR studies showed that the addition of 4-fluoro-3-methylphenol to **68** brougth to the formation of an equilibrium between **68** and a cationic five coordinate species, with the phenoxide stabilized by a hydrogen bond with the free phenol (Scheme 35). Similarly to **68**, addition of *t*-BuOH to **67** resulted in the formation of a cationic five-coordinate species in which the alkoxide interacts with the alcohol. Attempts to isolate the related isopropoxide Ru(O*i*-Pr)(CNN)(dppb) **37b** failed, on account of the slow conversion to the hydride RuH(CNN)(dppb), possibly through a β-hydrogen elimination reaction.

Eliminare spazio

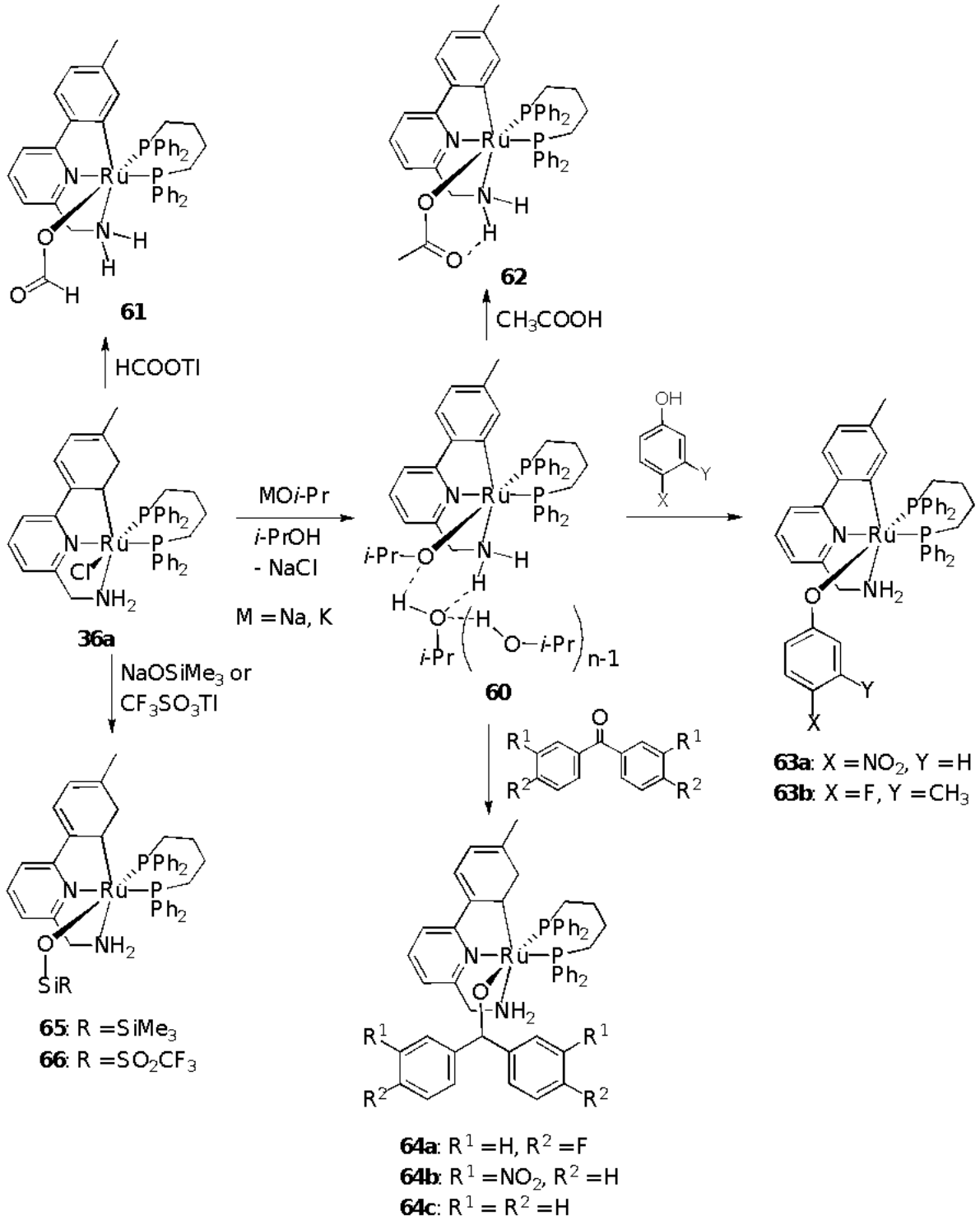
All the NH_2 complexes **61**–**66** showed to be highly active catalysts in the TH of acetophenone in 2-propanol with NaO*i*-Pr, affording complete conversion in a few minutes with only 0.005 mol% of catalyst, the best TOF (1.8×10^6 h^{-1}) was obtained with the the acetate complex **62** (Scheme 36). This catalyst proven to catalyze efficiently the quantitative reduction of other substrates with remarkably high TOF in the range of 1.7–3.8 x 10^6 h^{-1} (Scheme 37). On the other hand, complexes **67** and **68** displaying the NMe_2 group were poor catalysts in 2-propanol, leading to incomplete conversion of acetophenone (25–30% after 2 h), indicating that the presence of the NH_2 functionality is crucial for obtaining high performance.

Eliminare spazio

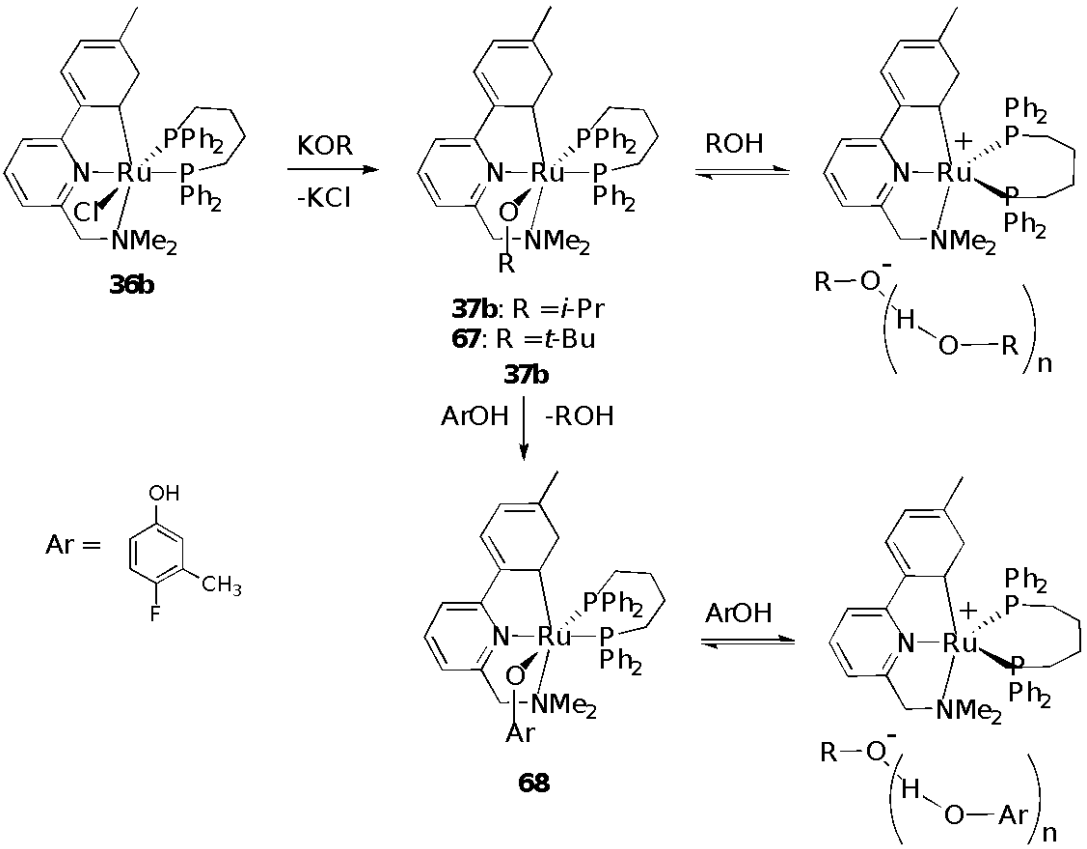
At 40 °C compounds **36a**, **64a** and **66**, are catalytically active in the TH with TOF of about 10^4 h^{-1}, indicating that the displacement of anionic ligand X (Cl, OAr, OSO_2CF3) by O*i*-Pr in 2-propanol is a rapid step even at low temperature (Scheme 36).

Eliminare spazio

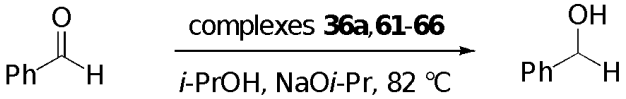
It is worth noting that the Ru-O pincer complexes **61**–**66** showed no catalytic activity without base and an excess of NaO*i*-Pr was crucial to achieve fast TH. These catalytic results suggested that, in basic 2-propanol solutions, the derivatives **61**–**66** are catalytic precursors and give rapid displacement of the oxygen-containing ligand, affording the catalytically active hydride RuH(CNN)(PP) (i.e. **38a**) and isopropoxide species Ru(O*i*-Pr)H(CNN)(PP) (i.e. **60**).



Scheme 34. Synthesis of the Ru-complexes **60**–**66**.



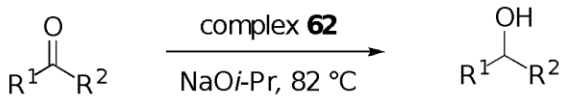
Scheme 35. Synthesis of the Ru-complexes **37b, 67** and **68**.



complex	conv (%)	time (min)	TOF (h^{-1})
61	97	2	1.4×10^6
62	97	2	1.8×10^6
63a	98	5	1.1×10^6
63b	96	5	6.0×10^5
64a	98	5	1.0×10^6
64b	98	5	8.7×10^5
64c	97	5	8.0×10^5
65	98	5	9.4×10^5
66	98	5	9.3×10^5
36a[a]	94	2 h	2.3×10^4
64a[a]	92	2 h	1.8×10^4
66[a]	92	2 h	2.1×10^4

Reaction conditions: acetophenone (0.1 M) in 2-propanol, with Ru-complex (Ru = 0.005 mol%, NaO*i*-Pr = 2 mol%) at 82 °C. [a]Reaction carried out at 40 °C.

Scheme 36. TH of acetophenone by using the Ru-complexes **36a**, **61**–**66**.



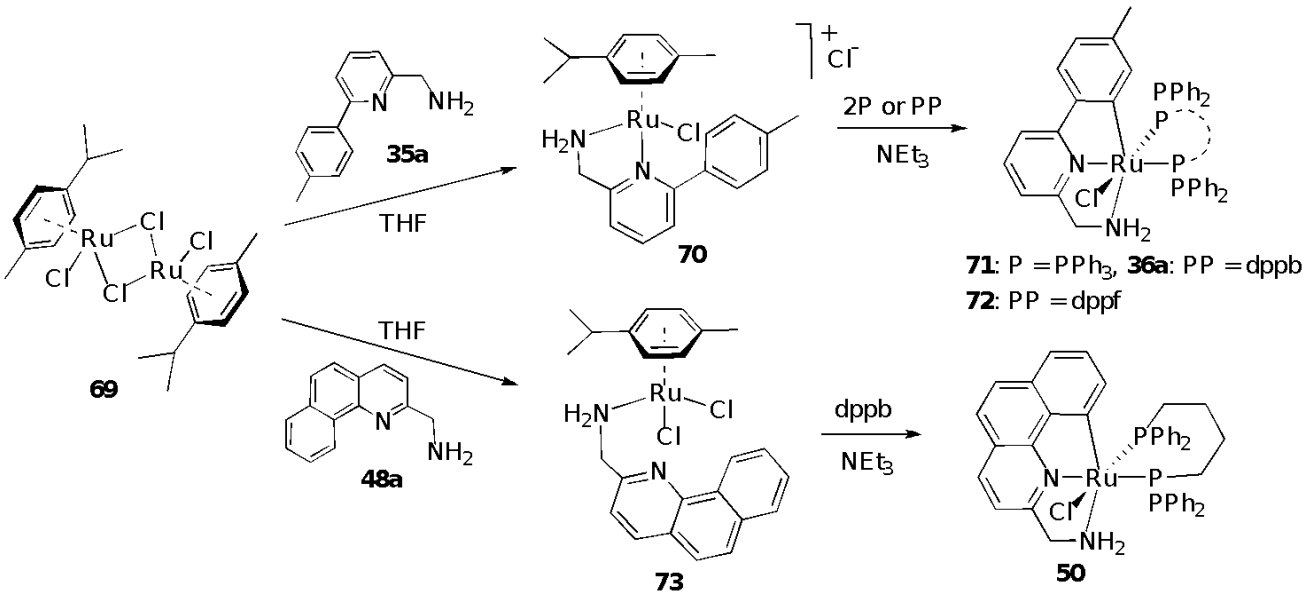
R^1	R^2	conv (%)	time (h)	TOF (h^{-1})
Me	3-BrC_6H_4	99	30 sec	3.8×10^6
Me	2-naphthyl	96	40 sec	3.7×10^6
-$CH_2(CH_2)_3CH_2$-		97	1	1.7×10^6
Me	CH_2=$CHCH_2CH_2$	96	2	1.1×10^6

Reaction conditions: ketone (0.1 M), complex (0.005 mol%), NaO*i*-Pr (2 mol%) at 82 °C.

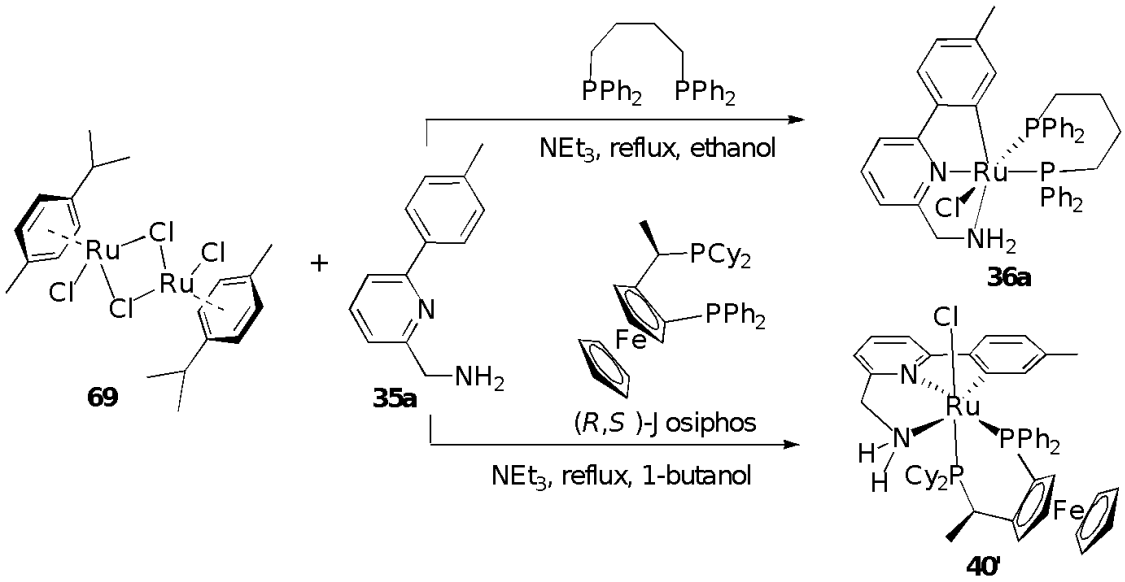
Scheme 37. TH of ketones using the Ru-complex **62**.

We very recently reported a practical route for the preparation of CNN pincer catalysts starting from [RuCl(μ-Cl)(η^6-*p*-cymene)]$_2$ (**69)** (Scheme 38 and 39) [39]. Treatment of **69** with 2 equiv of the ligand **35a** in THF promptly led to the cationic complex [RuCl(η^6-*p*-cymene)(**35a**)]Cl (**70**) in 81% yield (Scheme 38). The complex **70** reacted with PPh_3 in the presence of NEt_3 in ethanol at reflux to give the pincer compound **71** through displacement of *p*-cymene and orthometalation of **35a** (Scheme 38). Under the same reaction conditions, **70** reacted with dppb or dppf leading in high yield to **36a** or **72** respectively. Analogously, treatment of **69** with **48a** afforded the neutral benzo[h]quinoline derivative **73**, which by reaction with dppb in ethanol at reflux gave the pincer complex **50** in 80% yield (Scheme 38).

Interestingly, the complex **36a** was also obtained in 64% yield by adding **35a** and dppb to the Ru-precursor **69** in ethanol at reflux and in the presence of NEt_3, through a one pot synthesis and without isolating the intermediate **70** (Scheme 39). Following this procedure, treatment of **69** with **35a** and (*R*,*S*)-Josiphos in refluxing 1-butanol afforded the chiral pincer complex **40''** as a single stereoisomer in 62% yield (Scheme 39).



Scheme 38. Synthesis of the Ru-complexes **36a**, **50**, **70**-**73**.



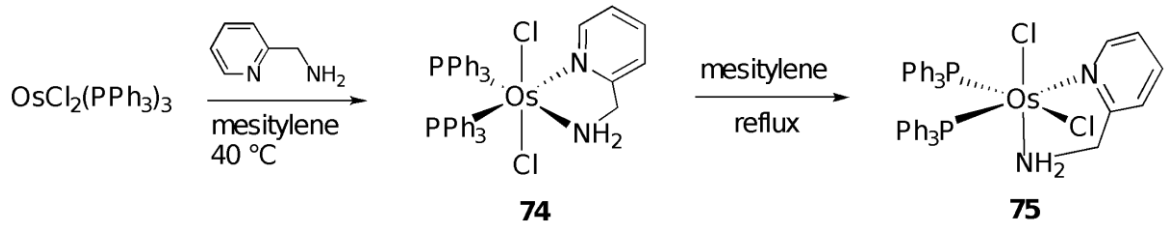
Scheme 39. Synthesis of the Ru-complex **36a** and **40' (40'** is the enatiomer of **40** (Scheme 26)).

2.2. Osmium complexes

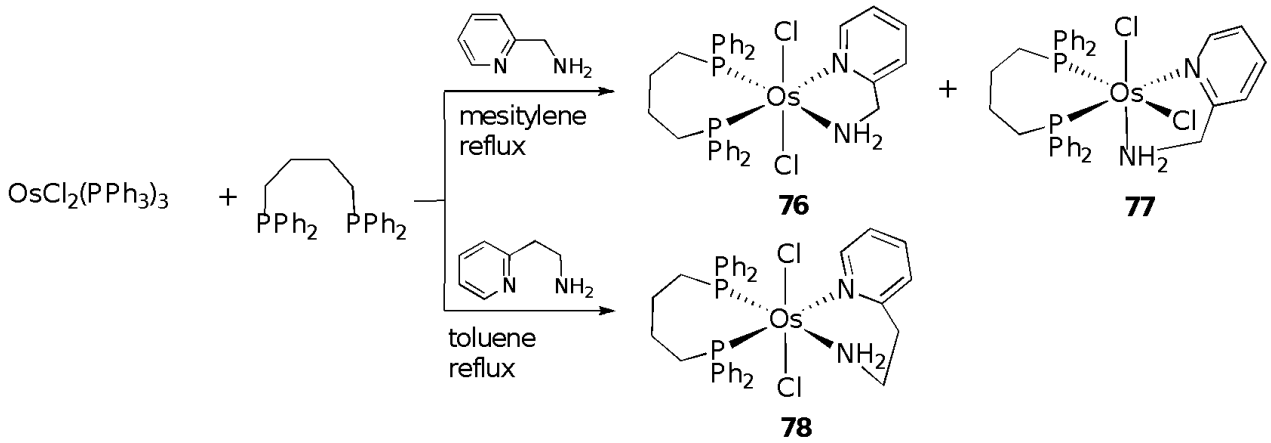
2.2.1. Bidentate NN Ampy-based osmium complexes

We described the preparation of a series of Ampy-based osmium complexes and their application in catalytic TH of carbonyl compounds [40]. Treatment of $OsCl_2(PPh_3)_3$ with one equivalent of Ampy in mesitylene at 40 °C led to the compound *trans,cis*-$[OsCl_2(PPh_3)_2(Ampy)]$ (**74**) (93% yield), which by prolonged heating afforded the complex **75** as a single specie (Scheme 40). Reaction of $OsCl_2(PPh_3)_3$ with one equivalent of dppb in CH_2Cl_2 and subsequent reaction with Ampy in mesitylene at 150 °C led to a mixture of *trans*-**76** and *cis*-**77** in about 1:3 molar ratio (Scheme 41). Employment of 2-(pyridin-2-yl)ethanamine, displaying a longer CH_2 chain than Ampy, resulted in the formation of *trans*-**78**

(Scheme 41).



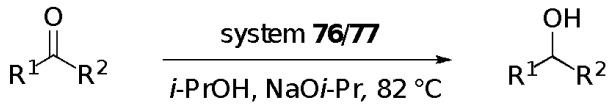
Scheme 40. Synthesis of the Os-complexes **74** and **75**.

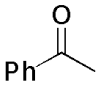
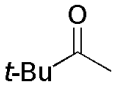
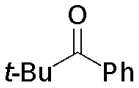
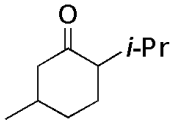
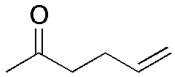


Scheme 41. Synthesis of the Os-complexes **76**,**77** and **78**.

Os-complexes **74**–**78** were catalytically active catalysts for TH of acetophenone in refluxing 2-propanol [40]. With the mixture **76**/**77**, TH of acetophenone occurred in 30s, leading to a TOF of 5.7 x 10^5 h^{-1} and so showing that its activity is higher than that of the analogue *trans*-$RuCl_2$(dppb)(Ampy) (**5**) and *cis*-$RuCl_2$(dppb)(Ampy) (**10**) (TOF = 3.5 x 10^4 and 3.0 x 10^5 h^{-1}, respectively) [17]. The system **76**/**77** enabled the fast reduction of different ketones (even bulky) and also the chemoselective reduction of 5-hexen-2-one, without reduction or isomerization of the terminal olefinic bond (Scheme 42).

Potresti aggiungere come prima linea i dati per acetophenone

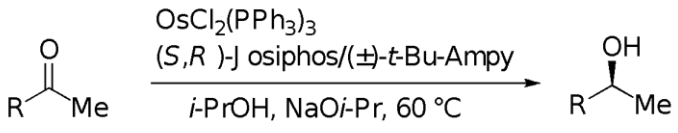


ketone	conv (%)	time (min)	TOF (h^{-1})
	98	30	5.7×10^5
	93	30	8.0×10^3
	98	30	1.7×10^4
	99	30	2.7×10^4
	96	2	3.2×10^5

Reaction conditions: ketone (0.1 M) with **76/77** (1:3 molar ratio)(Os 0.05 mol%) and NaO*i*-Pr (2 mol%) in 2-propanol at 82 °C.

Scheme 42. TH of ketones with the Os-system **76**/**77**.

With the catalyst generated *in situ* from $OsCl_2(PPh_3)_3$, (*S*,*R*)-Josiphos and Ampy or racemic 1-methyl(pyridin-2-yl)methanamine or 1-*t*-butyl(pyridin-2-yl)methanamine ((±)-R-Ampy, R = Me, *t*-Bu), ATH of acethophenone afforded (*S*)-1- phenylethanol with 91–95% ee and high TOF (up to 1.9×10^4) [40]. Comparable results were obtained by substitution of (*S*,*R*)-Josiphos with the bulkier (*S*,*R*)-Josiphos*. With the catalyst generated *in situ* from $OsCl_2(PPh_3)_3$, (*S*,*R*)-Josiphos and (±)-*t*-Bu-Ampy, ATH of aryl-methyl ketones afforded the related (*S*)-alcohols with 94–96% ee and TOF up to 1.2×10^4, indicating that this osmium system can be efficiently used for the preparation of chiral alcohols (Scheme 43).

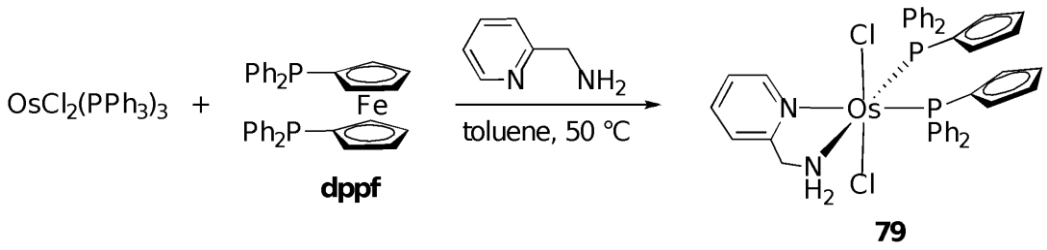


R	yield (%)	time (min)	ee (%)	TOF (h^{-1})
2-ClC_6H_4	99	30	94	1.2×10^4
2-$MeOC_6H_4$	98	60	95	9.1×10^3
2-MeC_6H_4	99	60	96	8.6×10^3

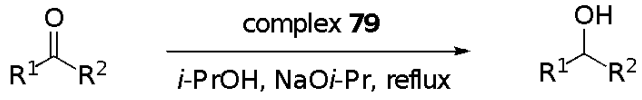
Reaction conditions: ketone (0.1 M), $[OsCl_2(PPh_3)_3]$/(*S*,*R*)-J osiphos/(±)-*t*-Bu-Ampy (Os 0.05 mol%) and NaO*i*-Pr (2 mol%) in 2-propanol at 60 °C.

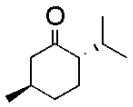
Scheme 43. ATH of ketones with $OsCl_2(PPh_3)_3$/(*S*,*R*)-Josiphos/(±)-*t*-Bu-Ampy.

We recently carried out a study to compare the ability of the Os-complex *trans*-$OsCl_2$(dppf)(Ampy) **79** (Scheme 44) and the related Ru-complex *cis*-$RuCl_2$(dppf)(Ampy) (**18**) (Scheme 10) to catalyze a variety of organic transformations involving ketones and alcohols [18]. Treatment of $OsCl_2(PPh_3)_3$ with 1 equiv of dppf in toluene at 50 °C (2 h), followed by addition of Ampy (2 h), afforded in 93% yield the osmium derivative *trans*-$OsCl_2$(dppf)(Ampy) **79** (Scheme 44). This complex catalyzed efficiently the selective TH of aldehydes and ketones to alcohols. By using a catalyst loading of 0.1−0.0005 mol% and in the presence of NaO*i*-Pr (2 mol%) in 2-propanol, quantitative conversion of several carbonyl compounds was achieved in a short time, affording TOF up to $3.0 \times 10^5\ h^{-1}$ at 82 °C (Scheme 45). The data reported in Scheme 45 indicate that the Os-complex efficiently catalyzes the reduction of aldehydes, with rates comparable to or even higher than those of the related Ru-complex 17 (Scheme 11).



Scheme 44. Synthesis of the Os-complex **79**.



R^1	R^2	conv (%)	time (min)	TOF (h^{-1})
Ph	H	98	5	3.0×10^5
4-$MeOC_6H_4$	H	98	5	1.8×10^5
n-C_5H_{11}	H	98[a]	30	6.0×10^3
$C_2H_5(CH_3)CH$	H	99	30	1.5×10^5
$(CH_3)_2C{=}CH(CH_2)_2CH(CH_3)CH_2$	H	98[a]	120	2.6×10^3
PhCH=CH	H	90[a]	120	8.9×10^4
Ph	Me	98	10	1.9×10^4
4-$MeOC_6H_4$	Me	87[b]	5	1.0×10^4
Ph	*t*-Bu	91[a]	60	4.7×10^3
Ph	Ph	98	60	7.8×10^4
$CH_2{=}CHCH_2CH_2$	Me	98[a]	5	4.3×10^4
		96[a]	10	4.6×10^4

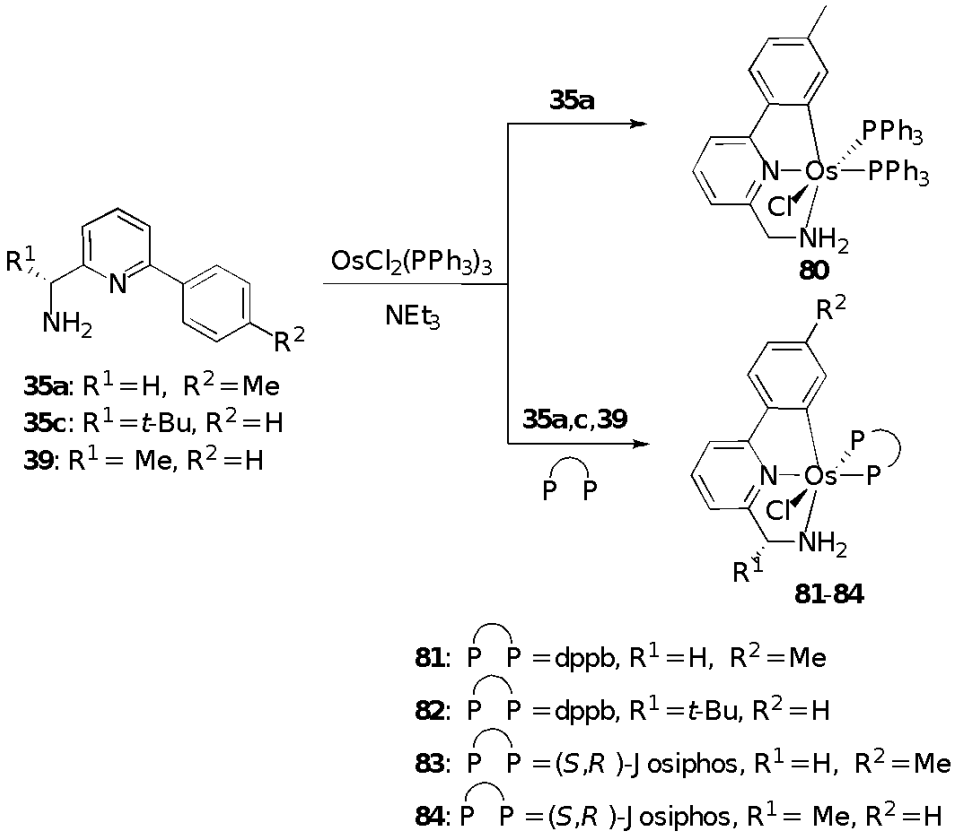
Reaction conditions: carbonyl compound (0.1 M), Ru-complex (0.005 mol%) with NaO*i*-Pr (2.0 mol%) in 2-propanol at reflux temperature. [a]Ru-complex 0.05 mol%. [b]Ru-complex 0.1 mol%.

Scheme 45. TH of aldehydes or ketones catalyzed by the complex **79**.

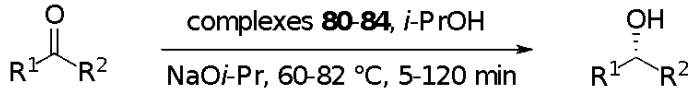
2.2.2. Tridentate CNN Ampy-based osmium complexes

We reported the isolation of a series of chiral pincer CNN Ampy-based osmium complexes and their application in catalytic asymmetric TH hydrogenation and HY of carbonyl compounds [41]. Treatment of $OsCl_2(PPh_3)_3$ with ligand **35a** (1.2 equiv) in 2-propanol in the presence of the weak base NEt_3 at reflux for 2 h affordded the CNN pincer complex **80** in 94% yield (Scheme 46). Complex **81** was easily obtained in high yield by treatment of $OsCl_2(PPh_3)_3$ with dppb and then with **35a** in the presence of NEt_3. The chiral pincer complex **82** was prepared in a similar manner to **81**, but with dppb in combination with **35c** (85% yield), while **83** and **84** (55 and 47% yield, respectively) were obtained from (*S*,*R*)-Josiphos with **35a** and **39**, respectively.

Pincer complexes **80**–**84** showed to be remarkably active catalysts for TH reduction of different types of ketones (Scheme 47). In 2-propanol and with NaO*i*-Pr (2 mol%) at 82 °C the TH was accomplished by a catalyst loading as low as 0.005 mol% with a TOF up to 1.3×10^6 h^{-1}. The ATH of methyl aryl ketones also proved to be possible with the chiral derivatives **82**–**84** (0.005 mol%) at 60 °C, affording enantioselectivities of up to 97% ee. Importantly, the unsaturated ketone hex-5-en-2-one could also be chemoselectively reduced to hex-5-en-2-ol (96% conversion) in 10 min at 82 °C (TOF = 4×10^5 h^{-1}).



Scheme 46. Synthesis of the Os-complexes **80**–**84**.



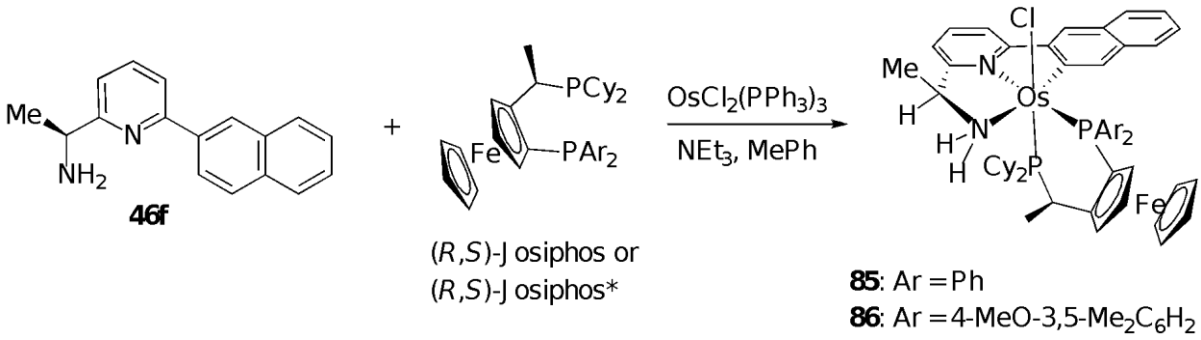
complex	R^1	R^2	temp (°C)	conv (%)	time (min)	TOF (h^{-1})	ee (%)
80	Me	Ph	82	96	10	1.8×10^5	
81	Me	Ph	82	98	5	1.3×10^6	
81	Me	2-ClC_6H_4	82	99	5	9.0×10^5	
81	-$CH_2(CH_2)_2CH_2$-		82	95	10	6.0×10^5	
81	Me	$CH_2CH_2CH{=}CH_2$	82	96	10	1.7×10^5	
82	Me	Ph	60	94	120	1.2×10^5	74
83	Me	Ph	60	95	30	1.7×10^5	83
84	Me	Ph	60	97	30	1.7×10^5	93
84	Me	2-$MeIC_6H_4$	60	92	60	4.0×10^4	91
84	Me	2-ClC_6H_4	60	96	30	1.3×10^5	90
84	Me	2-$MeOC_6H_4$	60	95	30	1.9×10^5	97
84	Me	3-$MeOC_6H_4$	60	94	10	2.0×10^5	97

Reaction conditions: ketone (0.1 M), complex (0.005 mol%) and NaO*i*-Pr (2 mol%) in *i*-PrOH.

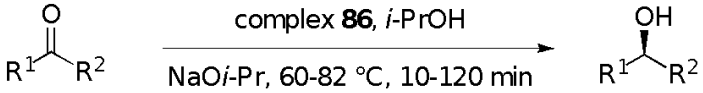
Scheme 47. TH of aromatic ketones catalyzed by the Os-complexes **80**-**84**.

The *in situ* generated pincer complexes OsCl(CNN)(PP), prepared from $OsCl_2(PPh_3)_3$, (*R*,*S*)-Josiphos* and ligands **39**,**46a**–**f** efficiently catalyzed the TH of acetophenone in 2-propanol at 60 °C and in the presence of NaO*i*-Pr [36]. The best ligand was the 2-naphthyl ligand (*S*)-**46f** that afforded (*R*)-1-

phenylethanol in 96% conversion with 87% ee and TOF = 1.5 x 10^5 h^{-1}. On the basis of these data, the complexes **85** and **86** were prepared from (*R*,*S*)-Josiphos and (*R*,*S*)-Josiphos* in combination with (*S*)-**46f** (Scheme 48). Complex **86**, which displayed to be a better catalyst than **85** for TH of acetopheneone, was also assessed for TH of alkyl (hetero)aryl ketones giving up to 99% ee and TOF = 10^5-10^6 h^{-1} (Scheme 49).



Scheme 48. Synthesis of the Os-complexes **85** and **86**.



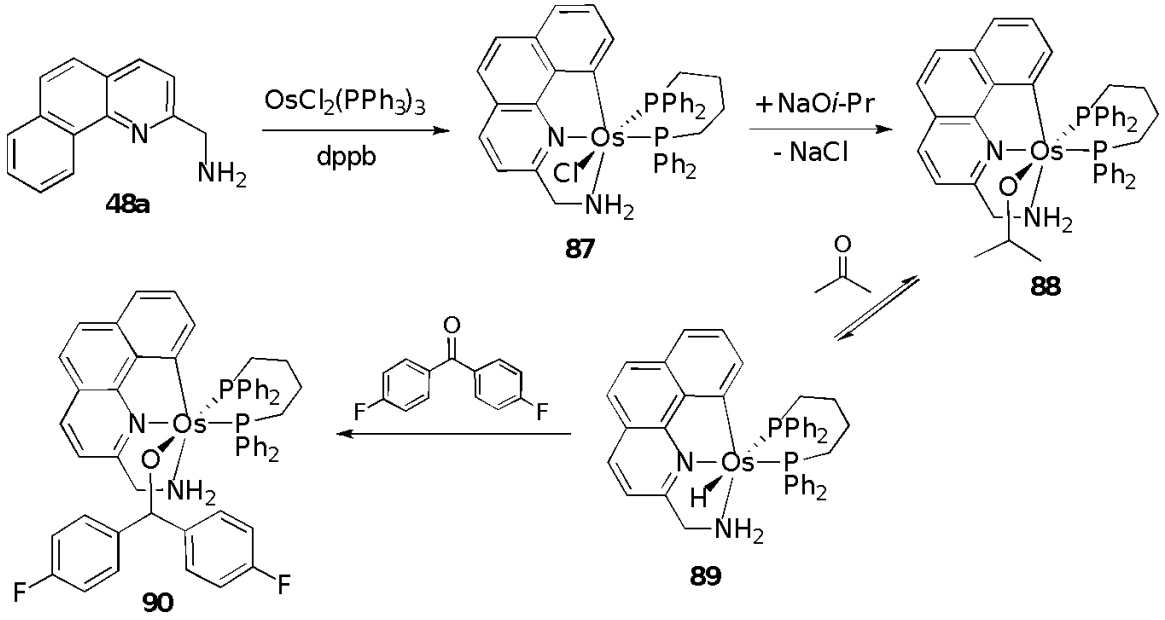
R^1	R^2	conv (%)	time (min)	TOF (h^{-1})	ee (%)
Me	Ph	97	30	3.2 x 10^5	91
Et	Ph	93	30	1.4 x 10^5	99
Me[b]	1-naphthyl	98	30	5.9 x 10^4	96
Me	2-naphthyl	97	10	3.4 x 10^5	99
Me	2-MeC_6H_4	93	60	5.9 x 10^4	94
Me[a]	3-ClC_6H_4	97	5	4.8 x 10^5	99
Me	3-$F_3CC_6H_4$	99	20	1.8 x 10^5	94
Me	3-$MeOC_6H$	97	30	2.0 x 10^5	99
Me[a,c]	3,5-$(MeO)_2C_6H_3$	97	10	9.0 x 10^5	97
Me[b,d]	3,5-$(F_3C)_2C_6H_3$	99	30	5.1 x 10^4	98
Me	2-pyridyl	99	30	1.2 x 10^5	91
Me[d]	3-pyridyl	99	30	7.6 x 10^4	90
Me[b,d]	4-pyridyl	99	10	8.3 x 10^4	97

Reaction conditions: ketone (0.1 M), complex (0.005 mol%), NaO*i*-Pr (2 mol%) in *i*-PrOH, 60 °C. [a]Reaction carried out at 82 °C. [b]Substrate/complex/NaO*i*-Pr = 10000/1/200. [b]Reaction carried out at 82 °C. [c]Substrate/complex/NaO*i*-Pr = 50000/1/1000. [d]In situ reaction.

Scheme 49. ATH of aromatic ketones catalyzed by the Ru-complexes **86**.

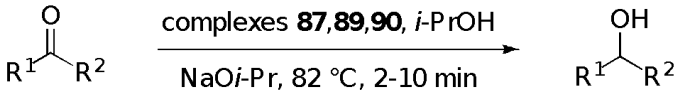
Pincer CNN osmium complexes based on the benzo[h]quinoline framework for TH catalysis have been next described by us (Scheme 50) [37]. For these CNN ligands a higher conformational rigidity is expected compared to those based on 2-phenylpyridine, due to the presence of the planar tricyclic

system. The thermally stable Os-complex **87** was easily prepared in quantitative yield by treatment of $OsCl_2(PPh_3)_3$ with dppb in CH_2Cl_2 at room temperature and by further reaction with 2-aminomethylbenzo[h]qunoline (**48a**) in the presence of NEt_3 in 2-propanol at reflux temperature (3 h) (Scheme 50). The Os-complex **87** reacted with NaO*i*-Pr (1.2 equiv) in 2-propanol/toluene (1:1 in volume) at 35 °C (3 h) affording a dark red solution containing the alkoxide **88** and the hydride **89** in 5:1 molar ratio (Scheme 50). The oxygen-sensitive hydride **89** was easily obtained in 74% yield by evaporation of the alcohol media and elimination of acetone. The mixture **88**/**89**, obtained from **87** and NaO*i*-Pr, rapidly and quantitatively reacted with bis(4-fluorophenyl)methanone, affording the Os-alkoxide **90** (Scheme 50).



Scheme 50. Synthesis of the Os-complexes **87**–**90**.

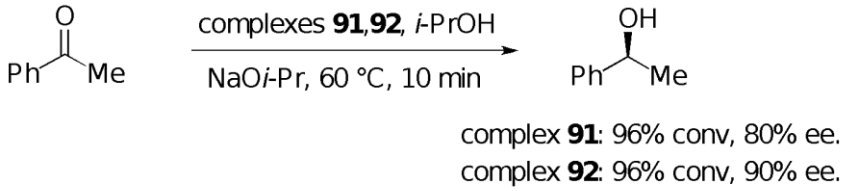
Complexes **87**–**90** were efficient catalysts for TH of ketones with 2-propanol in the presence of NaO*i*-Pr (2 mol%) (Scheme 51). TOF up to 1.8 x 10^6 h^{-1} were achieved by using 0.005 mol% of the catalyst. The air sensitive Os-H and Os-OR derivatives displayed significantly lower activity with respect the Os-Cl derivative. On the other hand, much the same activity was observed for the Os-Cl and the analogues Ru-Cl, -H, -OR derivatives [37]. The species *in situ* generated from $OsCl_2(PPh_3)_3$, (*S*,*R*)-Josiphos and 2-aminomethylbenzo[h]quinoline afforded the reduction of acetophen one to the (*S*)-alcohol with 80% ee and higher rate (TOF = 2.1 x 10^5 h^{-1} at 60 °C) compared to the related Ru-complex (Scheme 52) [37]. Furthermore, the use of the bulky (*S*,*R*)-Josiphos* resulted in an increase of the enantioselectivity (90% ee of (*S*)-alcohol (Scheme 52).



complex	R^1	R^2	conv (%)	time (min)	TOF (h^{-1})
87	Me	Ph	96	5	1.3×10^6
87	Me	2-$MeOC_6H_4$	99	2	1.8×10^6
87	Me	$CH_2CH_2CH{=}CH_2$	97	10	3.0×10^5
87	-$CH_2(CH_2)_3CH_2$-		98	5	7.0×10^5
89	Me	Ph	97	5	6.1×10^5
90	Me	Ph	99	5	8.1×10^5

Reaction conditions: ketone (0.1 M), complex (0.005 mol%), NaO*i*-Pr (2 mol%) in *i*-PrOH at 82 °C.

Scheme 51. TH of aromatic ketones catalyzed by the Ru-complexes **87**,**89** and **90**.



91: $OsCl_2(PPh_3)_3$, (*S*,*R*)-J osiphos and 2-aminomethylbenzo[h]quinoline; Os/PP/ligand = 1:1.5:2

92: $OsCl_2(PPh_3)_3$, (*S*,*R*)-J osiphos* and 2-aminomethylbenzo[h]quinoline; Os/PP/ligand = 1 :1.5:2

Scheme 52. TH of aromatic ketones catalyzed by the *in situ* formed Ru-complexes **91** and **92**.

3. Hydrogenation by molecular hydrogen of aldehydes and ketones

The catalytic hydrogenation (HY) of the polar C=O bond with hydrogen catalyzed by ruthenium complexes has been extensively investigated in the last decade and represents a core reaction for the synthesis of alcohols [42].

3.1. Ruthenium complexes

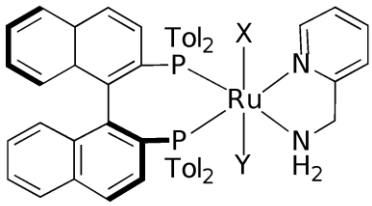
3.1.1. Bidentate NN Ampy-based ruthenium complexes

In 2005 ruthenium complexes based on the ligand Ampy for ketone HY were reported by the Noyori [43] and Morris [44] groups.

Eliminare spazio

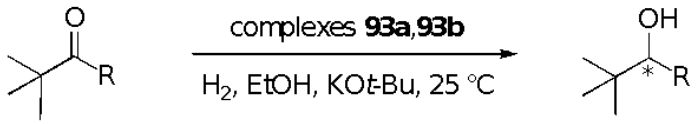
Noyori and co-workers to overcome the inefficiency of RuX_2(binap)(1,2-diamine) complexes to reduce *tert*-alkyl ketones, developed the Ru-complex **93a**,**b** (Fig. 6), which efficiently catalyzed the asymmetric hydrogenation (AHY) of sterically congested ketones to the related chiral alcohols. $RuCl_2$[(*S*)-tolbinap](Ampy) [(*S*)-**93a**] was conveniently synthesized by treatment of oligomeric

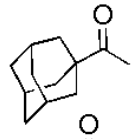
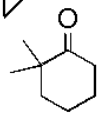
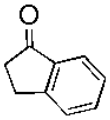
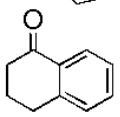
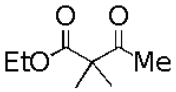
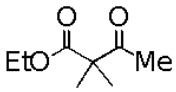
$RuCl_2$[(*S*)-tolbinap](dmf)$_n$ with 1.2 equiv of Ampy in CH_2Cl_2 at 25 °C for 2 h [43]. Five diastereomers were possible for this octahedral Ru complex, but the content of the most dominant diastereomer could be increased to >90% by heating at 80 °C for 30 min in toluene. The diastereomeric mixture was used as a precatalyst since the variable diastereomeric ratio did not affect the catalytic efficiency and enantioselectivity. Reaction of (*S*)-**93a** with 16 equiv of $NaBH_4$ in a 1:1 ethanol/benzene mixture afforded RuH(η^1-BH_4)[(*S*)-tolbinap](Ampy) [(*S*)-**93b**]. Under optimized reaction conditions, aliphatic, aromatic, heteroaromatic and olefinic ketones, as well as cyclic ketones, were re duced (Scheme 53). The reaction proceeded smoothly under mild conditions (1-20 atm, room temperature) with substrate/catalyst molar ratio as high as 100 000, affording chiral *tert*-alkyl carbinols with up to 98% ee. The higher activity in comparison to the conventional BINAP/1,2-diamine complexes was ascribed to the functional/structural characteristics of Ampy. The bidentate ligand has a functional NH_2 group and an unfunctional flat, small-sized pyridine ring that mitigates the repulsion with the *tert*-butyl group of an approaching ketone. Notably, the BINAP/Ampy Ru- catalyst was suitable only for reaction of *tert*-alkyl ketones. Thus, hydrogenation of acetophenone with (*S*)-**3a** gave (*R*)-1-phenylethanol in 100% yield, but with only 54% ee in ethanol or 14% ee in 2-propanol.



(*S*)-**93a**: X = Y = Cl
(*S*)-**93b**: X = H, Y = BH_4

Fig. 6. Chemical structure of the complexes (*S*)-**93a**,**b**.



R	catalyst	S/C[a]	H_2 (atm)	time (h)	yield (%)	ee (%)	conf
Me	(*R*)-**93a**	2000	1	9	100	88	*R*
Me	(*S*)-**93b**	2000	4	5	100	97	*S*
n-C_8H_{17}	(*R*)-**93a**	2300	5	5	100	97	*S*
i-Pr	(*S*)-**93a**	2020	8	24	<5	nd	nd
Ph	(*S*)-**93a**	2000	5	12	100	97	*R*
2-furyl	(*R*)-**93b**	2400	8	5	99	97	*R*
2-thienyl	(*S*)-**93a**	2100	8	5	100	98	*R*
(*E*)-CH=CHPh	(*S*)-**93a**	2050	5	5	100	97	*S*
(*E*)-CH=CH*n*-C_6H_{13}	(*S*)-**93b**	2040	8	5	99.6	98	*R*
	(*S*)-**93a**	2000	5	5	100	98	*S*
	(*S*)-**93a**	2250	8	5	95	84	*S*
	(*R*)-**93b**	2050	8	20	99.6	90	*S*
	(*R*)-**93a**	2400	8	5	100	98	*S*
	(*S*)-**93a**	2000	5	5	100	97	*S*
	(*S*)-**93b**	2000	5	5	100	82	*S*

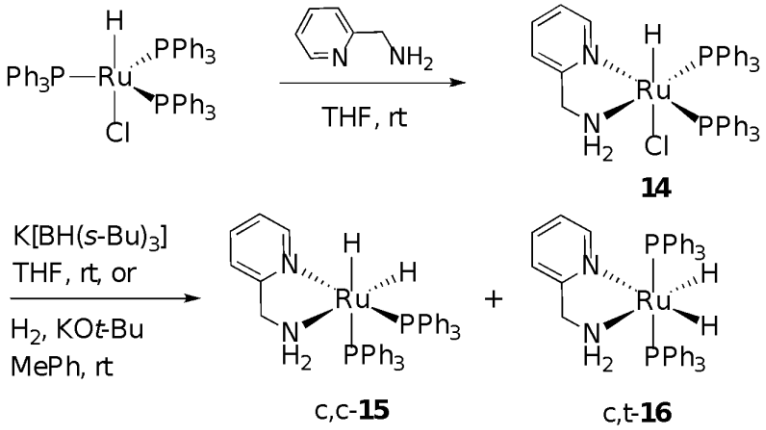
Reaction conditions: ketone (0.26-0.93 M) in ethanol containing the complex (0.10-0.53 mM) and KO*t*-Bu (20-28 mM) at 25-27 °C. [a]Substrate/catalyst molar ratio.

Scheme 53. AHY of sterically hindered ketones catalyzed by Ru-complexes **93a** and **93b**.

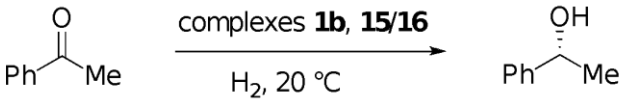
Morris [44] and we [17] in 2005 studied the formation of the mono- and di-hydride Ru-PPh_3-Ampy complexes which are involved in the HY and TH of ketones. Thus, the Ru-monohydride complex $RuHCl(PPh_3)_2$(Ampy) **14** (with Cl *trans* to H) was prepared by addition of 1 equiv of Ampy to $RuHCl(PPh_3)_3$ in THF (Scheme 54). Treatment of **14** with K[BH-(*sec*-Bu)$_3$] in THF or KO *t*-Bu/H_2 in toluene resulted in the formation of a mixture of highly reactive and air-sensitive Ru-dihydride isomer complexes. One is the dihydride *cis,cis*-**15** that has PPh_3 *trans* to H and PPh_3 *trans* to N(pyridyl), and another is the dihydride *cis,trans*-**16** with *trans* PPh_3 groups . The isomer *cis,cis*-**15** slowly converts to *cis,trans*-**16** in solution. The same behaviour was described indipendently by us

using NaiOPr for the conversion of **15** to the **16** species via acetone elimination (Scheme 9). The reaction of **14** with KO*t*-Bu under argon resulted in the formation of a mixture that includes a complex with an imino ligand HN=CH-2-py, while the same reaction under H_2 led to **15** and then **16**.

The mixture of the isomers **15/16** was a very active catalyst for the hydrogenation of neat acetophenone to 1-phenylethanol at room temperature and 3 atm H_2 (Scheme 55). An active catalyst system was also obtained starting from complex **14** and KO*i*-Pr. Notably, the mixture **15/16** showed in benzene a lower catalytic activity than the **14**/KO*t*-Bu mixture.



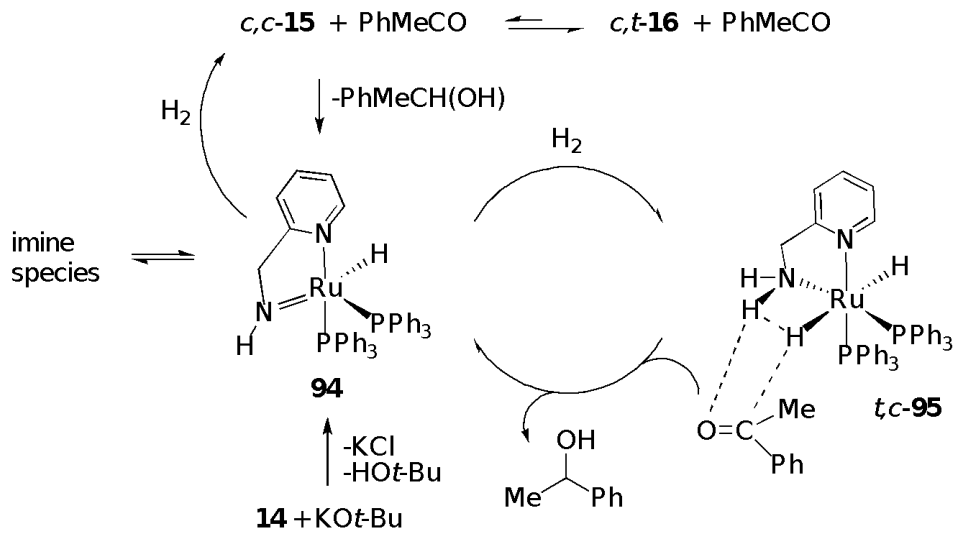
Scheme 54. Synthesis of the Ru-complexes *c,c*-**15** and *c,t*-**16**.



precatalyst	solvent	H_2 (atm)	base	ketone:Ru:base	time/conv
15/16 = 18/72	--	3	--	2000:1	1 h/100%
14	--	3	KO*i*-Pr	2000:1:8	1 h/100%
15/16 = 7/83	HPh	5	--	709:1	1.3 h/12%
14	HPh	5	KO*t*-Bu	709:1:17	1.3 h/98%

Scheme 55. HY of acetophenone catalyzed by the Ru-complexes **14** and **15/16**.

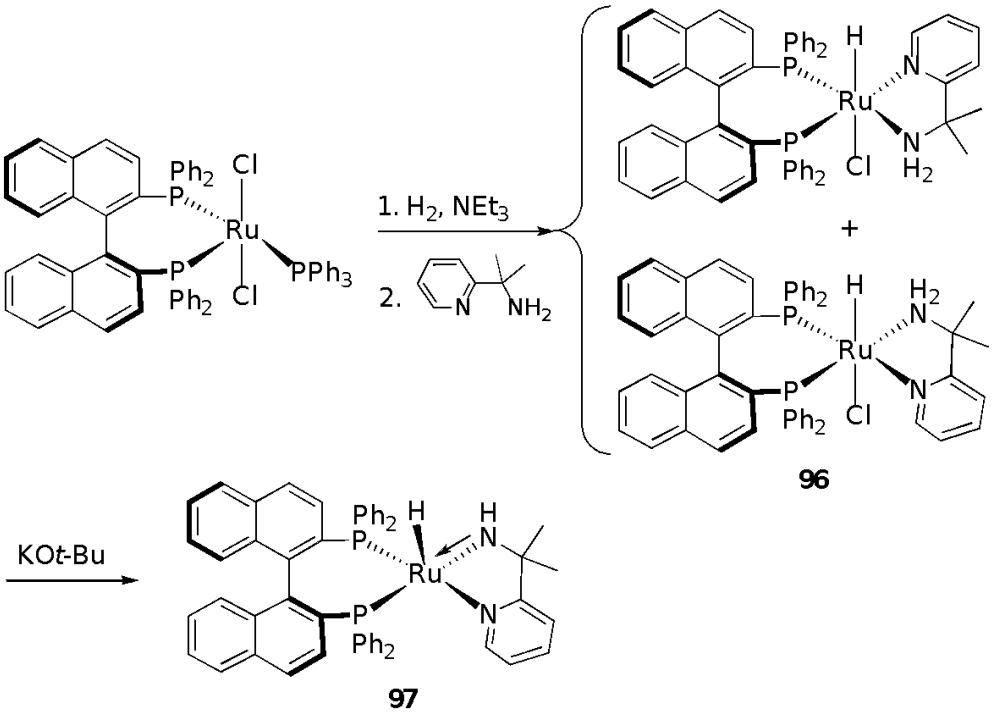
The mechanism of the hydrogenation reaction was thought to involve two very reactive species, the dihydride *trans,cis*-**95**, and the amido complex **94**, neither of which were however directly observed (Scheme 56). In the dihydrogen activation step, the amido complex **94** was proposed to split heterolytically an η^2-dihydrogen ligand into a hydride on ruthenium and a proton on nitrogen to regenerate the *trans*-dihydride complex. The *cis*-dihydride **15** reacted quickly with acetophenone to enter the catalytic cycle via **94** while the *cis*-dihydride with *trans*-PPh_3 groups, *cis,trans*-**16**, needs an activation step, probably isomerization to *cis,cis*-**15** to enter the cycle.



Scheme 56. Proposed mechanism for the HY of acetopheneone catalyzed by the Ru-complex **14**.

The same research group has also prepared Ru-catalysts by using the ligand 2-amino-2-(2-pyridyl)propane (AppH) that differs from Ampy by the presence of two methyl groups on the α-carbon [45]. This ligand was designed to block β-hydride elimination reactions.

When the complex RuHCl[(*S*)-binap)](PPh$_3$) was reacted with H_2 under basic conditions and then with AppH, the complex RuHCl[(*S*)-binap)](AppH) **96** was formed as a mixture of two diastereomers in about 9:1 ratio (Scheme 57). Complex **96** rapidly reacted with KO*t*-Bu, eliminating an equivalent of HCl, to produce the deep red hydridoamido complex Ru(H)(*S*-binap)(App) **97** (Scheme 57), which represented the first structure of a Ru-binap hydrido-amido complex. The crystal structure of **97** revealed a five-coordinate Ru(II) center with a short Ru-N(amido) distance (1.962(3) Å) and a trigonal planar geometry at the amido nitrogen.



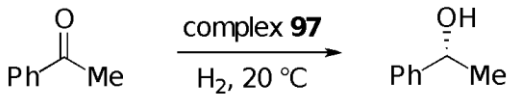
Scheme 57. Synthesis of the Ru-complexes **96** and **97**.

Complex **97** showed to be an active catalyst for HY of acetophenone in 2-propanol without base (TOF > 6700 h^{-1} at 20 °C, 5 atm H_2), but afforded a lower activity in TH from the same solvent under comparable conditions (TOF 110 h^{-1} at 20 °C, 1 atm Ar) (Scheme 58).

Kinetic experiments using **97** as a catalyst and acetophenone as the substrate in benzene showed that the rate of 1-phenylethanol production was dependent on both Ru and H_2 concentrations. Moreover, the initial rate was not depending on the substrate concentration. These observations on experiments at low ketone conversions and therefore low alcohol concentrations suggested to the authors the sequence of events as shown in path a of Scheme 59. The amido complex **97** heterolytically cleaves the H_2 molecule into a hydride on the metal and a proton on the amido nitrogen to afford *trans*-RuH_2[(*S*)-binap)](AppH) **98** (not observed), which is responsible for the addition of H^-/H^+ to the C=O bond of the substrate to give (*R*)-1-phenethanol in about 27% ee. However, it was also noted that the product concentration affected the hydrogenation rate as confirmed by adding *rac*-1-phenylethanol to the reaction mixture prior to the hydrogenation. Thus, the alcohol was supposed to assist the H_2 splitting via a six-membered transition state shown in path b of Scheme 59. In this scenario the alcohol protonates an amido nitrogen, while the H_2 molecule is heterolytically cleaved between a Ru(II) center and an oxygen atom of the alkoxide, likely this protonation-cleavage process occurs simultaneously through a hydrogen-bonded network.

Density functional theory (DFT) calculations on a model amido complex confirmed that the splitting of H_2 to give the *trans* dihydride is the turnover-limiting step and lies 9 kcal/mol in free energy above

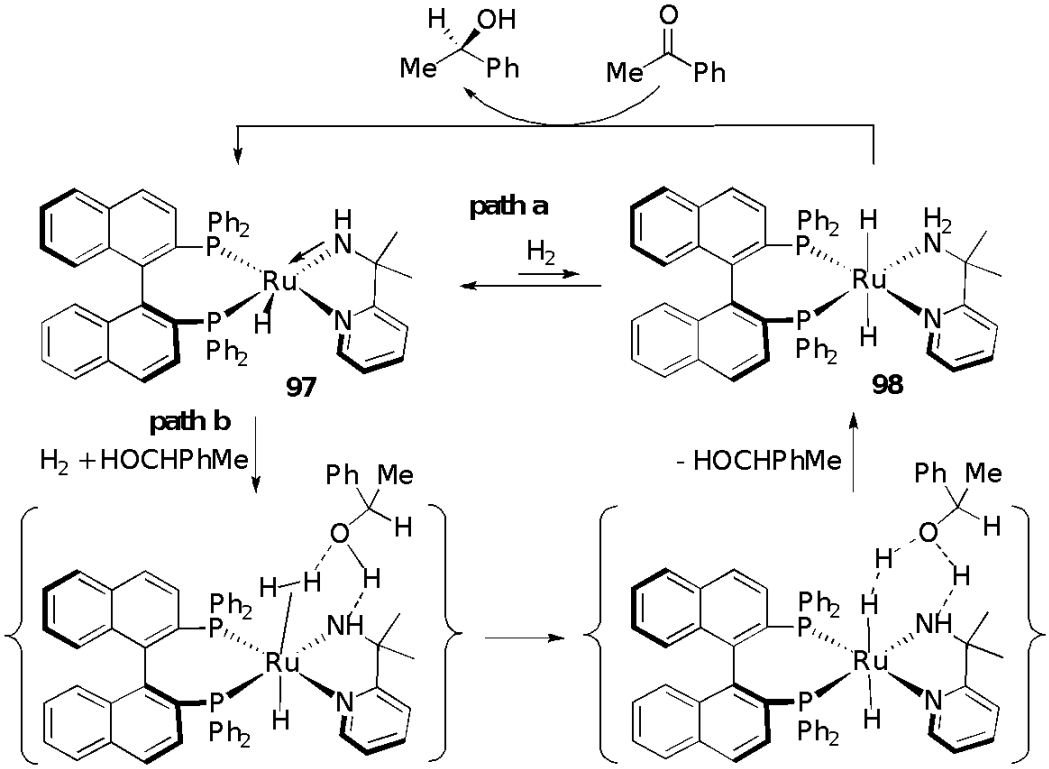
the transition state for the ketone hydrogenation step. The formation of the dihydride is entropically unfavorable. The theoretical activation barrier for H_2 splitting is lowered by 5 kcal/mol by an alcohol-assisted mechanism but still remains higher in energy than the ketone hydrogenation step. This latter step can also be alcohol-assisted and can result in a different ee in the product alcohol than without alcohol assistance, as observed experimentally for reactions using 2-propanol versus benzene as the solvent. With alcohol present, an alkoxohydridoruthenium(II) complex is calculated to be the catalyst resting state.



solvent	additive	HY or TY	TOF (h^{-1})	ee (%)
benzene	none	HY	550	25-27
benzene	*rac*-$C_6H_5CH(OH)CH_3$ (0.04 M)	HY	1520	--
benzene	2-propanol (0.06 M)	HY	1150	29
2-propanol	none	HY	6750	32
2-propanol	none	TY	115	37

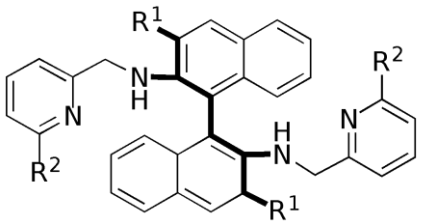
Reaction conditions: complex (0.0003 M), acetophenone (0.18 M) and H_2 (5 atm) at 20 °C.

Scheme 58. HY of acetophenone by the Ru-complex **97**.



Scheme 59. Proposed simplified mechanism for the hydrogenation of acetophenone catalyzed by **97** in benzene with low concentrations of alcohol (path a) and high concentrations of alcohol (path b).

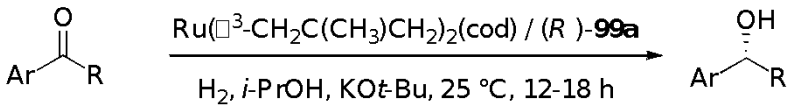
Kitamura and co-workers reported the application in aromatic ketones HY of a catalytic system consisting of a π-allyl Ru-precursor and a sp^2N/sp^3N combined ligands **99**, synthesized from 1,1'-binaphthyl-2,2'-diamine on the basis of an *ortho*-lithiation-halogenation-Suzuki-Miyaura coupling protocol (Fig. 7) [46]. The catalytic activity as well as the enantioselectivity in HY of acetophenone was initially investigated by using ligands (*R*)- **99a-c** in combination with the series of Ru-precursors **100**–**103** ($Ru(\pi\text{-}CH_2C(CH_3)CH_2)_2(cod)$ (**100**), $[RuCl_2(cod)]_n$ (**101**), $[RuCl_2(C_6H_6)]_2$ (**102**) and Ru(cod)(cot) (**103**)) in the presence of KO*t*-Bu and 50 atm of H_2 at 25 °C (Scheme 60). Under these reaction conditions, (*R*)-**99a** and **100** afforded the best results, giving (*R*)-1-phenylethanol in 99% yield and with 93% ee after 15 h. With this catalytic system a variety of ketones were submitted to hydrogenation. An electron-donating substituent, such as OCH_3 and CH_3, at the *para* position of the benzene ring of acetophenone increased the enantiomeric excess up to 98%, while this value was lowered to 80% by introduction of the electron-withdrawing CF_3 group. 2-Acetonaphthone was also hydrogenated in good yield and enantioselectivity. With primary and secondary alkyl- phenyl ketones, the enantiomeric excess ranged from 94 to 98%, but the presence of a tertiary alkyl group decreased it to 86%. Cyclic aromatic ketones were converted to the corresponding *R* alcohols in 93-99% ee. 1-Indanone was not hydrogenated under the standard conditions, but gave 1-indanol with 93% ee without the use of KO*t*-Bu.



(*R*)-**99a-c**

a: $R^1 = Ph$, $R^2 = H$; **b**: $R^1 = R^2 = H$
c: $R^1 = H$, $R^2 = Me$

Fig. 7. Chemical structure of *N,N*-bidentate ligands (*R*)-**99a**–**c**.

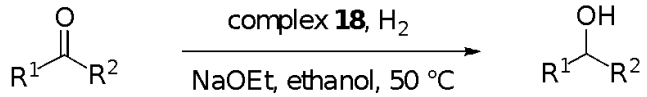


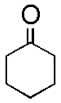
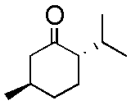
Ar	R	yield (%)	ee (%)
Ph	Me	99	93
Ph	Me	99	94[a]
Ph	Me	99	94[b]
4-$MeOC_6H_4$	Me	99	98
4-MeC_6H_4	Me	99	96
4-$CF_3C_6H_4$	Me	99	80
2-naphthyl	Me	99	95
Ph	$MeCH_2$	99	98
Ph	$Me(CH_2)_7$	99	94
Ph	Me_2CH	99	98
Ph	*c*-C_6H_{11}	99	97
Ph	Me_3C	99	86
-C_6H_4-2-$(CH_2)_4$-		99	94
-C_6H_4-2-$(CH_2)_3$-		99	99
-C_6H_4-2-$(CH_2)_2$-		99	93[c]

Reaction conditions: ketone (2 M), (*R*)-**99a** (2 mM),Ru(□-$CH_2C(CH_3)CH_2)_2$(cod) (2 mM), KO*t*-Bu (2 mM), H_2 (50 atm) *i*-PrOH, 25 °C, 12-18 h. [a]No base, 48 h. [b](*R*)-**99a** = 0.2 mM, 66 h. [c]Ketone = 400 mM, no base.

Scheme 60. AHY of aromatic ketones catalyzed by (*R*)-**99a**-Ru(π-$CH_2C(CH_3)CH_2)_2$(cod).

We have recently carried out a study to compare the ability of the Ru-complex *cis*-$RuCl_2$(dppf)(Ampy) **18** (Scheme 10) and the related Os-complex *trans*-$OsCl_2$(dppf)(Ampy) **79** (Scheme 44) to catalyze a variety of organic transformations involving ketones and alcohols [18]. Complex **18** showed to be catalytically active in HY of aldehydes and ketones at low hydrogen pressure (5 atm) (Scheme 61). With **18** (0.1−0.02 mol%) a rapid HY occurred in ethanol at 30−50 °C in the presence of NaOEt (2 mol%), affording TOF up to 7.5 x 10^4 h^{-1}.



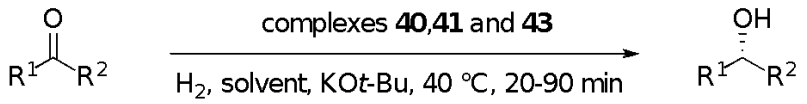
R^1	R^2	conv (%)	time (min)	TOF (h^{-1})
Ph	H	99	10	7.5×10^4
4-$MeOC_6H_4$	H	95	5	5.0×10^4
$PhCH_2$	H	98	10	9.1×10^3
PhCH=CH	H	98	60	2.8×10^4
Ph	Me	93[a]	60	5.4×10^3
4-$MeOC_6H_4$	Me	98	60	7.0×10^3
Ph	4-ClC_6H_4	95[a]	5 h	2.7×10^3
		94	60	2.5×10^4
		35	3 h	

Reaction conditions: carbonylic compound (0.5 M), NaOEt (2 mol%) in ethanol with the Ru-catalyst (0.1 mol%) under 5 atm of H_2. [a]Reation carried out at 30 °C.

Scheme 61. HY of carbonyl compounds catalyzed by the Ru-complex **18**.

3.1.2. Tridentate CNN Ampy-based ruthenium complexes

The Ru-complexes **40**, **41** and **43** (Scheme 26) were found to efficiently catalyze the AHY of ketones in ethanol or methanol/ethanol under 5 atm of dihydrogen in the presence of KO*t*-Bu (6 mol%) (Scheme 62) [35]. However, it was noted hat the alcohol solvent plays an important role in the HY vs TH. Employing complex **41** the addition of methanol to ethanol resulted in a decrease in the rate and an increase of the enantioselectivity. Conversely, with **43** the addition of MeOH led to an increase in both activity and enantioselectivity. Thus, in methanol the reduction had to be regarded as pure HY, affording (*S*)-1-phenylethanol with 89% ee (78% conversion in 3 h), whereas in 2-propanol the *S* alcohol was formed by TH with a negligible contribution from HY (91% ee and 75% conversion) [35]. By using a MeOH/EtOH=1/1 mixture, the complex **43** showed to rapidly catalyze the reduction of acetophenone by HY to give (*S*)-1-phenylethanol with 90% ee (99% within 30 min). Analogously, other ketones were reduced to the corresponding *S* alcohols within 30 min (TOF of up to 3.8×10^4 h^{-1}) and with high enatioselectivities (90-99% ee) (Scheme 62).



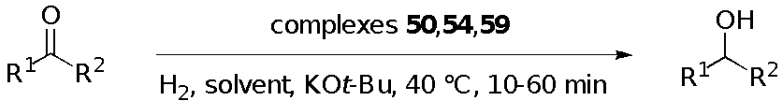
complex	R^1	R^2	solvent	conv (%)	time (min)	TOF (h^{-1})	ee (%)
40	Me	Ph	EtOH	>99	30	4.3×10^4	70
41	Me	Ph	EtOH	99	30	3.6×10^4	71
41	Me	Ph	MeOH/EtOH = 1	94	90	2.5×10^4	88
43	Me	Ph	EtOH	>99	60	1.7×10^4	77
43	Me	Ph	MeOH/EtOH = 1	>99	30	3.3×10^4	90
43	Me	3-MeC_6H_4	MeOH/EtOH = 1	99	20	3.8×10^4	93
43	Me	4-MeC_6H_4	MeOH/EtOH = 1	99	30	3.0×10^4	90
43	Me	2-$MeOC_6H_4$	MeOH/EtOH = 1	>99	30	2.9×10^4	91
43	Me	2-naphthyl	MeOH/EtOH = 1	>99	30	3.6×10^4	93
43	Et	Ph	MeOH/EtOH = 1	>99	30	2.5×10^4	99

Reaction conditions: H_2 (5 atm), ketones (0.5 M), complex (0.02 mol%), KO*t*-Bu (6 mol%) at 40 °C.

Scheme 62. AHY of aromatic ketones catalyzed by the Ru-complexes **40**, **41** and **43** .

We found that the Ru-complexes **50**,**54** (Scheme 30) and **59** (Scheme 31) were found to be active in the HY of ketones with H_2 at low pressure (Scheme 63) [47]. By carrying out the reaction in methanol at 40 °C and in the presence of KO*t*-Bu (base/Ru = 200), the derivative **50** and **59** catalyzed the quantitative reduction of different ketones in 30-60 min with TOF up to 3.1×10^4 h^{-1} and a substrate/Ru ratio of 10000. Questa frase è riportata a nel capitolo “Hydrogenation .. of imines” pag 74

AHY of acetophenone was achieved with **54** (S/Ru = 10000) in the presence of KO*t*-Bu at 40 °C, affording in a methanol/ethanol mixture (7:3) and in 30 min quantitative formation of (*S*)-1-phenyl-ethanol with 92% *ee* (TOF = 4.3×10^4 h^{-1}) (Scheme 63). With this complex other alkyl- aryl ketones were reduced with success (up to 99% ee), whereas the aliphatic ketone 2-eptanone was quantitatively hydrogenated, but with poor enantioselectivity (42% *ee*).



complex	R^1	R^2	conv (%)	time (min)	TOF (h^{-1})	ee (%)
50[a]	Me	Ph	99	30	3.1×10^4	
50[a]	Me	*n*-C_5H_{11}	99	60	3.0×10^4	
50[a]	Me	$CH_2CH_2CH{=}CH_2$	95	60	1.4×10^4	
50[a]	-$CH_2(CH_2)_3CH_2$-		99	60	1.9×10^4	
59[a]	Me	Ph	98	30	2.9×10^4	
54[b]	Me	Ph	99	30	4.3×10^4	92 (*S*)
54[b]	Me	2-ClC_6H_4	95	60	1.6×10^4	90 (*S*)
54[b]	Me	3-$MeOC_6H_4$	99	60	1.6×10^4	94 (*S*)
54[b]	Me	3-BrC_6H_4	99	10	5.5×10^4	91 (*S*)
54[b]	Me	4-MeC_6H_4	96	60	3.1×10^4	92 (*S*)
54[b]	Me	2-naphthyl	95	30	5.6×10^4	93 (*S*)
54[b]	Et	Ph	97	60	2.0×10^4	99 (*S*)
54[b]	Me	*n*-C_5H_{11}	99	60	1.8×10^4	42 (*S*)

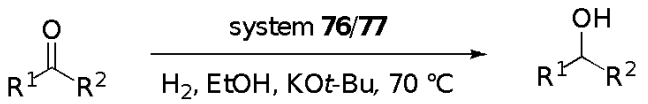
Reaction conditions: [a]ketone (0.5 M) in MeOH, under H_2 (5 atm) at 40 °C, substrate/Ru/KO*t*-Bu = 10000:1:200. [b]Ketone (0.5 M) in MeOH/EtOH (7:3), under H_2 (5 atm), at 40 °C, substrate/complex/KO*t*-Bu = 10000:1:200.

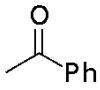
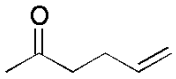
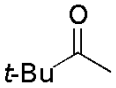
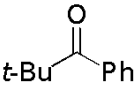
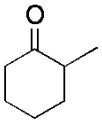
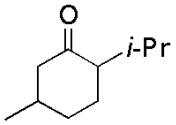
Scheme 63 . HY of aromatic ketones catalyzed by the Ru-complexes **50**,**54** and **59**.

3.2. Osmium complexes

3.2.1. Bidentate NN Ampy-based osmium complexes.

The catalytic activity of the Os-system **76**/**77** (1:3 molar ratio) (Scheme 41) in HY of ketones at low dihydrogen pressure was examined (Scheme 64) [40]. Among the different alcohols (MeOH, EtOH and *i*-PrOH), ethanol was found to give the best performance in the presence of KO*t*-Bu. Thus, when an ethanol solution of acetophenone (0.5 M) containing **76**/**77** (Os 0.05 mol%) and KO*t*-Bu (2 mol%) was stirred under 5 atm of H_2 at 70 °C, complete reduction of acetophenone was achieved in 10 min (TOF = 1.5×10^4 h^{-1}). At a lower loading of osmium (0.005 mol%), the reduction occurred completely with almost the same rate, indicating that **76**/**77** is a robust catalytic system for HY. This system also catalyzed efficiently the hydrogenation of other ketones including bulky *tert*-butyl substrates (Scheme 64).

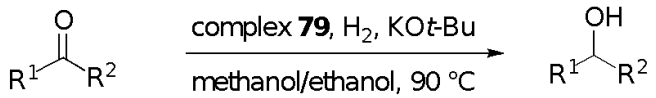


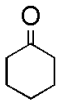
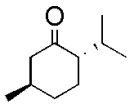
complex (mol%)[a]	ketone	conv (%)	time (h)	TOF (h^{-1})
0.05 0.01 0.005		>99 >99 >99	10 min 1 4	1.5×10^5 1.4×10^4 1.3×10^4
0.01		>99	1	1.4×10^4
0.01		>99	3	1.1×10^4
0.01		97	2	1.1×10^4
0.01		99	3	7.0×10^4
0.01		>99	2	1.3×10^4

Reaction conditions: ketone (0.5 M), KO*t*-Bu (2 mol%), ethanol, H_2 (5 atm) at 70 °C. [a]Mixture **76**/**77** = 1:3

Scheme 64. HY of ketones by the Os-system **76**/**77**.

Complex **79** (Scheme 44) was catalytically active in the HY of aldehydes and ketones at low hydrogen pressure (5 atm) (Scheme 65) [18]. With **79** (0.1 mol%) good performances were achieved in a methanol/ethanol mixture (3/1, v/v) by using KO*t*- Bu (2 mol%) at 90 °C leading to complete conversion of the substrate in 10 minutes or hours (8 h) (TOF up to 1.0×10^4 h^{-1}). Comparative results between catalyst **79** and the related Ru-complex **18** (Scheme 65 vs Scheme 10) suggested that that osmium is a valid complement to ruthenium for both HY and TH reactions, taking into account that osmium is more robust and generally requires a slightly higher temperature to become catalytically active.



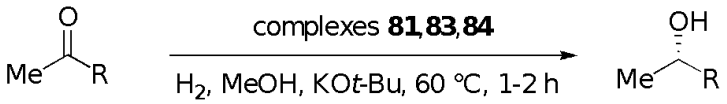
R^1	R^2	conv (%)	time (min)	TOF (h^{-1})
Ph	H	97	10	1.0×10^3
4-$MeOC_6H_4$	H	97	30	4.7×10^3
$PhCH_2$	H	91	8 h	1.0×10^3
PhCH=CH	H	90	30	4.6×10^3
Ph[a]	Me	98	10	9.0×10^3
4-$MeOC_6H_4$	Me	95	30	3.7×10^3
Ph	4-ClC_6H_4	97	30	4.6×10^3
		99	15	6.8×10^3
		90	2 h	3.7×10^3

Reaction conditions: carbonyl compound (0.5 M), KO*t*-Bu (2 mol%) in methanol/ethanol (3/1, v/v) with the Os-catalyst (0.1 mol%) under 5 atm of H_2 at 90 °C.

Scheme 65. HY of ketones catalyzed by Os-complex **79**.

3.2.2. Tridentate CNN Ampy-based osmium complexes.

The Os-complexes **81**,**83** and **84** (Scheme 46) showed to be active catalysts for the HY of ketones in methanol with KO*t*-Bu under 5 atm of H_2 at 60 °C [41]. Thus, various ketones were quantitatively converted into the corresponding alcohols within 1-2 h in the presence of 0.005 mol% of the catalyst (TOF of up to 5.2×10^4 h^{-1}) (Scheme 66). AHY of methyl aryl ketones also proved possible with the chiral derivatives **83** and **84** (0.005 mol%) at 60 °C, affording enantioselectivities of up to 98% ee. These complexes were the first examples of Os-catalysts capable to give AHY of ketones and are among the most active and productive catalysts for HY of carbonyl compounds.

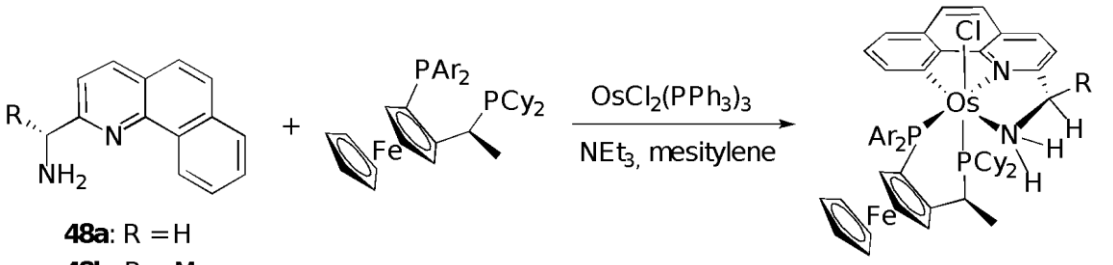


complex	R^1	R^2	conv (%)	time (h)	TOF (h^{-1})	ee (%)
81	Me	Ph	99	1	2.5×10^4	
81	Me	3-$MeOC_6H_4$	99	1	2.6×10^4	
81	-$CH_2(CH_2)_2CH_2$-		99	0.5	3.3×10^4	
81	Me	*n*-C_5H_{11}	99	1	2.9×10^4	
83	Me	Ph	98	0.5	5.2×10^4	80
84	Me	Ph	99	2	1.2×10^4	86
84	Me	2-$MeOC_6H_4$	99	2	2.2×10^4	93
84	Me	3-$MeOC_6H_4$	99	2	2.0×10^4	98
84	Me	3-ClC_6H_4	99	1	2.8×10^4	98

Reaction conditions: H_2 (5 atm), ketones (0.5 M), complex (0.005 mol%), KO*t*-Bu (5 mol%), MeOH.

Scheme 66. HY of aromatic ketones catalyzed by the Os-complexes **81**,**83** and **84**.

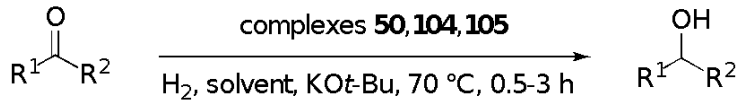
We also prepared chiral orthometalated osmium complexes, based on 2-aminomethylbenzo[*h*]quinoline ligands, that were used in the HY of ketones [47]. Treatment of $OsCl_2(PPh_3)_3$ with 1.2 equiv. of (*S*,*R*)-Josiphos in mesitylene at 110 °C (2 h) gave a mixture of uncharacterized products, which slowly reacted with 2-aminomethylbenzo[*h*]quinoline **48a** (1.4 equiv) in the presence of NEt_3 to afford complex **104** (24 h at 140 °C) in 67% yield (Scheme 67). Moreover, according to our previous studies on Ru- and Os-complexes, which showed that (*S*,*R*)-Josiphos correctly matched with chiral 1-substituted-1-(pyridin-2-yl)methanamines and CNN ligands of *R* configuration, we prepared the complex **105** as a single stereoisomer by reaction of $OsCl_2(PPh_3)_3$ with (*S*,*R*)-Josiphos* and (*R*)-**48b** (Scheme 67) [47]. The previously prepared Os-complex **49** and the new complexes **104** and **105** were found to be active in the HY of C=O bonds with H_2 at low pressure (Scheme 68). Os-complex **50** catalyzed the quantitative hydrogenation of various ketones at 70 °C under 5 atm H_2 with a low amount of base (KO*t*-Bu/Os = 5), affording a TOF up to 3.2×10^4 h^{-1}. The chiral Os-complexes **104** and **105** showed to hydrogenate acetophenone at 70 °C with 86 and 92% ee, respectively, and at a good rate (TOF up to 2.0×10^4 h^{-1}) in a MeOH/EtOH mixture and with a KO*t*-Bu/Os ratio of 200. Interestingly, a similar performance was reached with **104** prepared *in situ* from $OsCl_2(PPh_3)_2$/(*S*,*R*)-Josiphos*/**48a**, affording (*S*)-1-phenylethanol with 90% ee. With the unisolated complex **104** the reduction of other three ketones was achieved with up to 99% ee (Scheme 68).



48a: R = H
48b: R = Me

104: Ar = Ph, R = H
105: Ar = 4-MeO-3.5-$Me_2C_6H_2$
R = Me

Scheme 67. Synthesis of the Os-complex **104** and **105**.



complex	R^1	R^2	conv (%)	time (h)	TOF (h^{-1})	ee (%)
50[a]	Me	Ph	99	30	3.2×10^4	
50[a]	Et	Ph	99	30	2.7×10^4	
50[a]		*n*-C_8H_{17}	99	30	2.8×10^4	
50[a]	-$CH_2(CH_2)_3CH_2$-		99	30	2.8×10^4	
50[a]	-$CH(Me)(CH_2)_3CH_2$-		99	3 h	5.4×10^3	
104[b]	Me	Ph	99	30	2.0×10^4	86 (*S*)
105[b]	Me	Ph	97	60	1.4×10^4	92 (*S*)
in situ[c]	Me	Ph	99	30	2.4×10^4	90 (*S*)
in situ[c]	Me	3-$MeOC_6H_4$	99	30	2.2×10^4	91 (*S*)
in situ[c]	Me	2-naphthyl	99	30	1.6×10^4	94 (*S*)
in situ[c]	Et	Ph	99	60	1.3×10^4	99 (*S*)

Reaction conditions: [a]ketone (0.5 M) in MeOH, under H_2 (5 atm), substrate/Os/KO*t*-Bu = 10000:1:5 at 70 °C. [b]Ketones (0.5 M) in MeOH/EtOH (7:3), under H_2 (5 atm) at 70 °C, substrate/ complex/KO*t*-Bu = 10000:1:200. [c]Ketones (0.5 M) in MeOH/EtOH (7:3), under H_2 (5 atm) at 70 °C, $OsCl_2(PPh_3)_3$/(*S*,*R*)-J osiphos*/**48b** = 1:1.5:2.

Scheme 68. HY of aromatic ketones catalyzed by the Os-complex **49**, **104** and **105** or the *in situ* formed system $OsCl_2(PPh_3)_2$/(*S*,*R*)-Josiphos*/**48a**

3.2.3. Tridentate PNN Ampy-based osmium complexes

Very recently Gusev and co-workers reported the synthesis and application of the Os-complexes **106-108** and Ru-complex **109** in the catalytic hydrogenation of unsaturated carbonyls (Fig. 8) [48, Gusev]. In this group, the complex **106b** emerged as a successful chemoselective reduction catalyst. The air-stable **106b** was prepared according to Scheme 69. The related dihydrides $OsH_2(CO)$(NNNP-*t*Bu) **111** were formed when **106b** was treated in THF with Li($HBEt_3$), or with base under H_2 (via the 16-e amido species **110**). The dihydride **111** consits as a mixture of isomers in solution (*trans*/*cis* = 4/1, THF). The reaction of **110** with H_2 to give **111** is reversible, and about 17% of **110** was formed when **111** is

dissolved in THF. The Os-complex **106b** gave almost complete selectivity (92–100%) in the hydrogenation (H_2 = 50 bar, 23 to 100 °C) of the α,β-unsaturated aldehydes **A1**–**A4** (Fig. 9) and ketones **K1**–**K6** (Fig. 9) in a non-polar solvent and in the presence of a carbonate base (Scheme 70). In the case of 10-undecenal, the best selectivity was achieved with 0.2% CsF in 2-propanol.

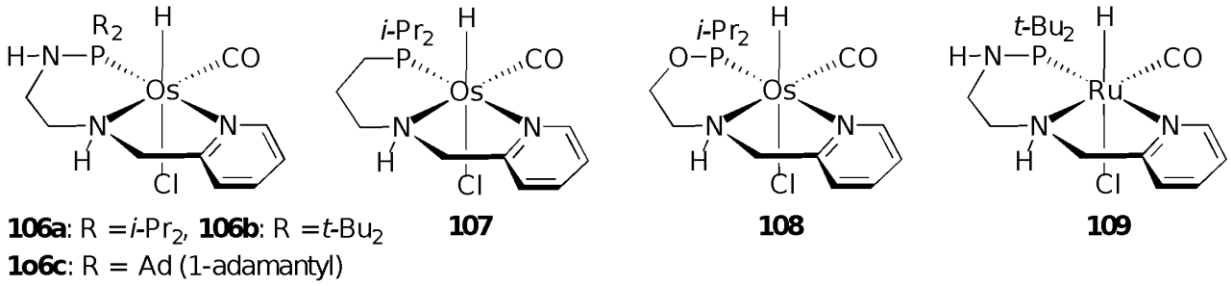
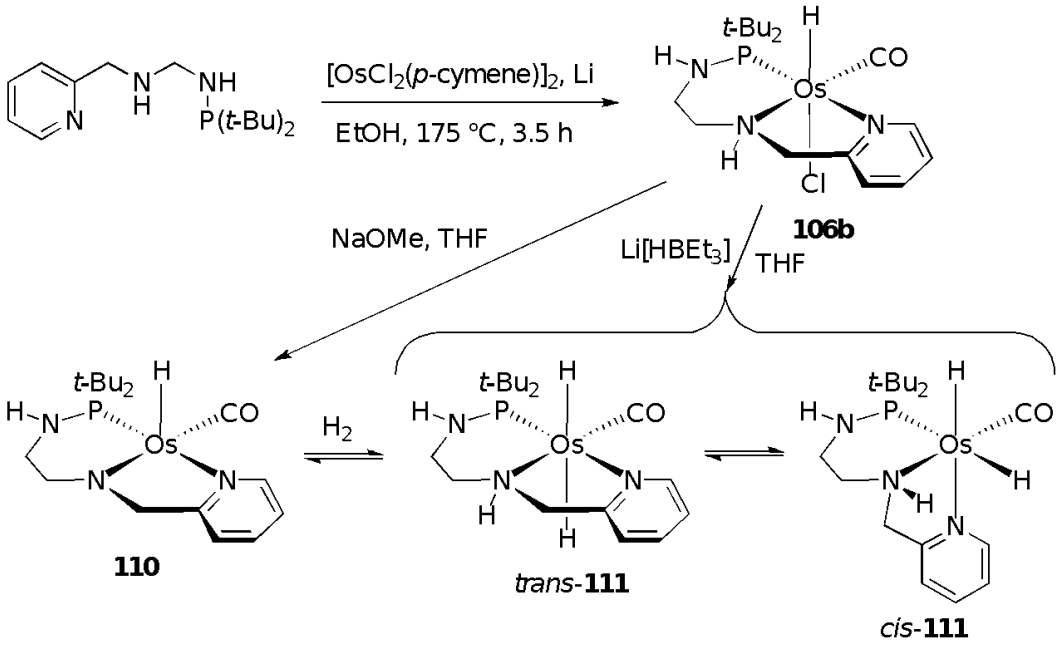


Fig. 8. Chemical structure of Os-complexes **106**–**108** and Ru-complex **109**.



Scheme 69. Synthesis of the Os-complexes **106b**,**110** and **111**.

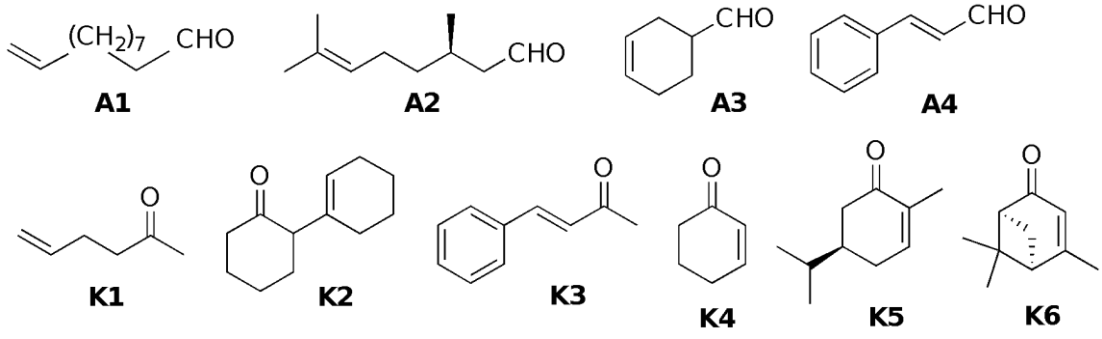
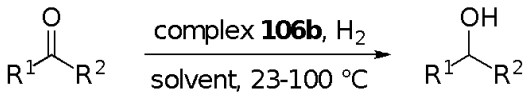


Fig. 9. Aldehydes and ketones used in the HY by the Os-complex **106b**.



s[a]	cat[b]	time (h)	solvent	base[c]	sel[d]	conv (%)[e]
A1, 40	0.05	1	*i*-PrOH	CsF, 0.2	>99	100[f]
A2, 20	0.05	2	THF	Cs_2CO_3, 1	100	100
A3, 20	0.05	3	THF	K_2CO_3, 3	100	100
A4, 20	0.05	2.5	THF	Cs_2CO_3, 1	100	>99
K1, 80	0.01	2	neat	K_2CO_3, 0.2	98	100
K2, 40	0.02	1	*i*-PrOH	K_2CO_3, 0.2	100	100
K3, 20	0.01	12	*i*-PrOH	Na_2CO_3, 1	98	100[g]
K4, 20	0.014	2	THF	Na_2CO_3, 1	92	100
K5, 20	0.01	9	THF	Na_2CO_3, 1	100	99
K6, 20	0.05	12	*i*-PrOH	Na_2CO_3, 1	100	100[h]

Reaction conditions: H_2 (50 bar), 100 °C. [a]Substrate, mmoles. [b]Catalyst, mol%. [c]Base, mol%. [d]Selectivity (100% when no C=C hydrogenation). [e]Total (saturated + unsaturated) conversion to alcohol. [f]At 80 °C. [g]At 23 °C. [h]At 60 °C.

Scheme 70. HY of the aldehydes **A1**–**A4** (Fig. 9) and ketones **K1**–**K6** (Fig. 9) by the Os-complex **106b**.

4. Mechanistic studies on hydrogen transfer and hydrogenation mediated by tridentate CNN Ampy-based Ru-complexes

We carried out mechanistic studies on CNN pincer ruthenium catalysts (CNN = 2-aminomethyl-6-arylpyridine based ligands) for HY and TH of ketones by NMR and kinetic measurements as well as computational methods. For these investigations the choice fell on the RuCl(CNN)(dppb) (dppb = $PPh_2P(CH_2)_4PPh_2$) system **36a**, which is simpler to investigate with respect to the well-known Noyori catalysts, (η^6-arene)RuCl((Tsdpen) (**112**)[10] and *trans*-$RuCl_2$(PP)(1,2-diamine) (**113**) [49] (Fig. 10). The presence in **36a** of only one chloride, which converts to a monohydride, and the pincer and diphosphine ligands, which stabilize the reactive intermediates, reduces the freedom degrees of this ruthenium system (e.g., isomerization at the metal center), facilitating the detection of the species involved in the catalysis, by NMR spectroscopy. Moreover, an important feature of **36a**, which shares with **112** and **113**, is to be a highly active catalyst both in TH and HY by changing the catalytic parameters (H_2 vs Ar atmosphere, solvent, base, temperature).

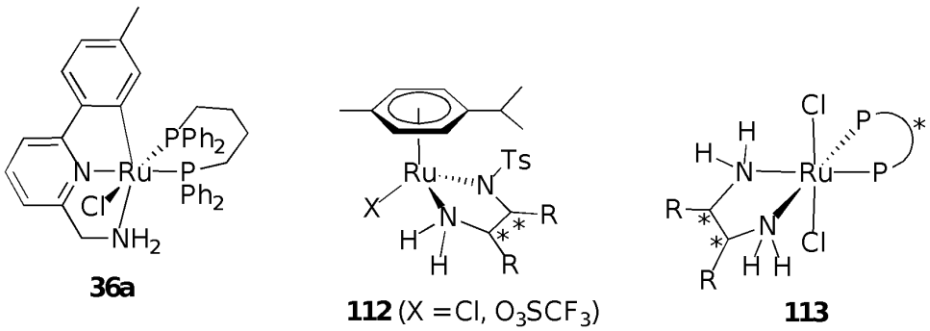
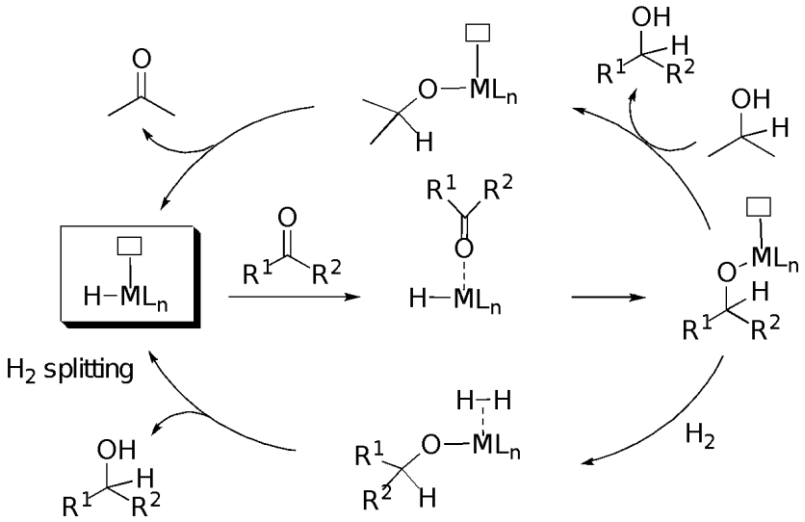


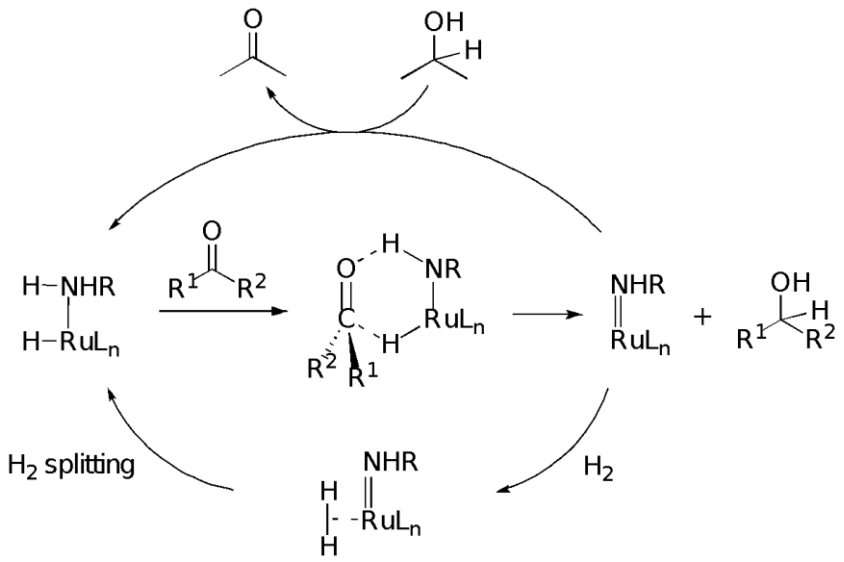
Fig. 10. Chemical structure of the complexes **36a**, **112** and **113**.

Metal hydrides are the key species involved in the catalytic TH and HY of carbonyl compounds [50]. In TH the M-H complexes are generated from a hydrogen donor, such as 2-propanol or formic acid, via cleavage of C-H bonds, while in HY these active species are formed from H_2 splitting. For these reactions both an inner- and an outer-sphere mechanism has been proposed. In the first mechanism a metal-hydride containing a *cis*-vacant site, reacts with the coordinated carbonyl substrate, affording a metal alkoxide intermediate via migratory insertion (Scheme 71). In the outer-sphere mechanism the substrate does not coordinate to the metal. Hydrogen (a hydride from the metal and a proton from the ligand) is transferred to the carbonyl compound in a concerted or step-wise manner via a six membered transition state. This mechanism has been demonstrated to occur for ruthenium complexes with a NH_2 functionality, such as complexes **112** in TH and **113** in HY (Scheme 72). In these cases the cis Ru-H and Ru-NH_2 moieties react with the substrate leading to the alcohol product and the Ru-amide, featuring a Ru–N double bond [11] (metal-ligand bifunctional catalysis [11].

Is worth pointing out that the type of mechanism (inner vs outer) is subtly controlled by small electronic differences at the metal center [51]. In addition, when the catalytic HY is performed in 2-propanol both HY and TH reactions can occur simultaneously.



Scheme 71. Reduction of carbonyl compounds through the inner-sphere TH and HY pathway.

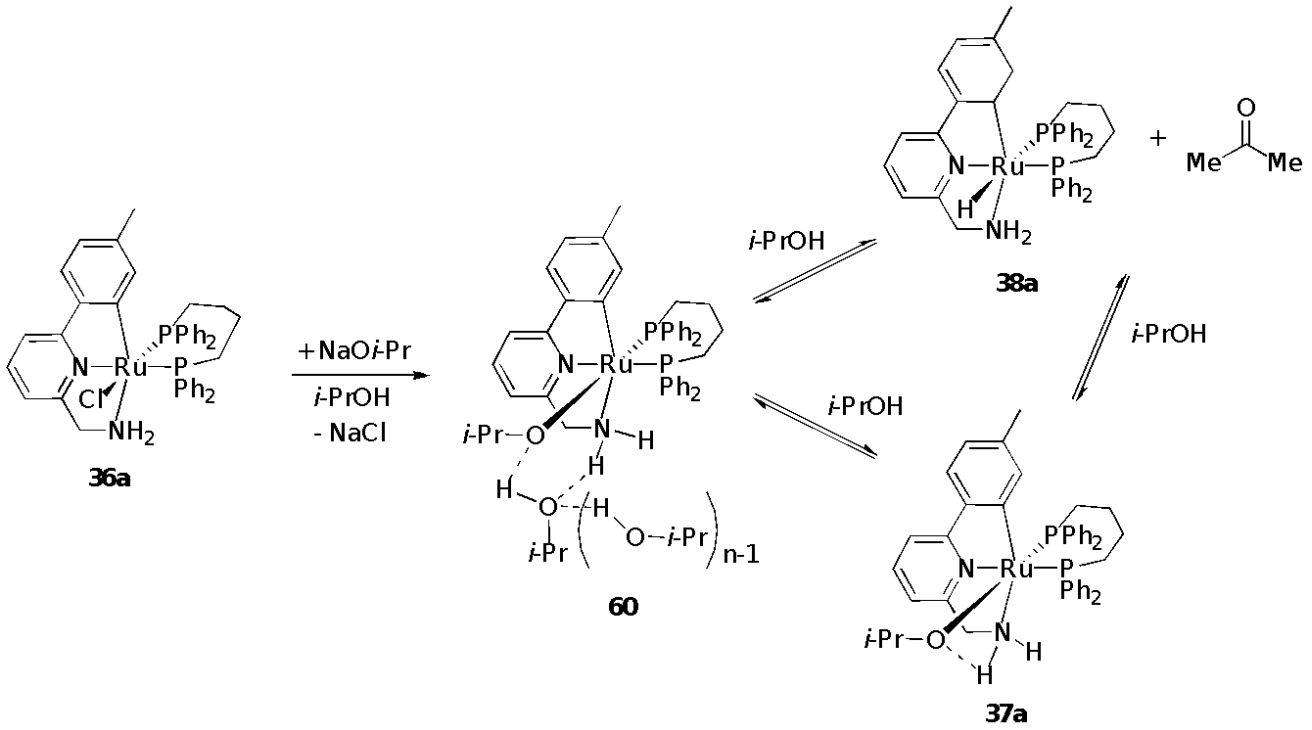


Scheme 72. Reduction of carbonyl compounds through the outer-sphere TH and HY pathway.

We found that the reaction of **36a** with sodium isopropoxide in 2-propanol/C_6D_6 afforded the alcohol-adduct alkoxide **60**, which is in equilibrium with the hydride **38a**/acetone mixture (Scheme 73) [52]. The hydride **38a** was isolated from **36a** and NaO*i*Pr in 2-propanol/toluene by evaporation of the alcohol media and elimination of acetone under reduced pressure [32]. The alkoxide **60** was alternatively formed by treating a suspension of **38a** in 2-propanol/C_6D_6 with acetone . When **38a** was reacted with acetone in C_6D_6 and in the absence of 2-propanol, the formation of the simple isopropoxide **37a** was observed by NMR spectroscopy. Moreover, ^{31}P-^{31}P NMR NOESY in solution revealed a rapid equilibrium between the alkoxide **37a** and **38a**/acetone mixture with an exchange rate of 2.9 ± 0.4 s^{-1}. Interestingly, the alkoxide **60** containing 2-propanol equilibrates with the hydride **38a** with a significant higher rate (5.4 ± 0.2 s^{-1}), showing that that alcohol has a crucial role in enhancing the rate of exchange process [52].

Substitution in **36a** of the NH_2 group with the NMe_2 function **36b** produced a poorly active TH catalyst [32b]. Stoichiometric reaction of **36b** with NaO*i*Pr in *i*PrOH gave a species analogous to **37a**, which slowly and irreversibly converts to the ruthenium hydride **36b** [32b]. These results indicate that the NH_2 group in combination with 2-propanol plays both a thermodynamic and a kinetic role (1) by stabilizing the alcohol adduct **60** vs the hydride **38a** and (2) increasing the rate of β-hydrogen elimination vs the ketone insertion reaction. Thus, the effect of the Ru-NH_2 function in enhancing the rate of the catalytic TH of ketones was ascribed to its ability to form a hydrogen-bonding network with 2-propanol and alkoxides, leading to the alcohol adducts **60**, which equilibrates quickly with the hydride **38a**. A similar behavior was also observed for the analogous Os-complex Os(CNN)(OiPr)(dppb) [37,41].

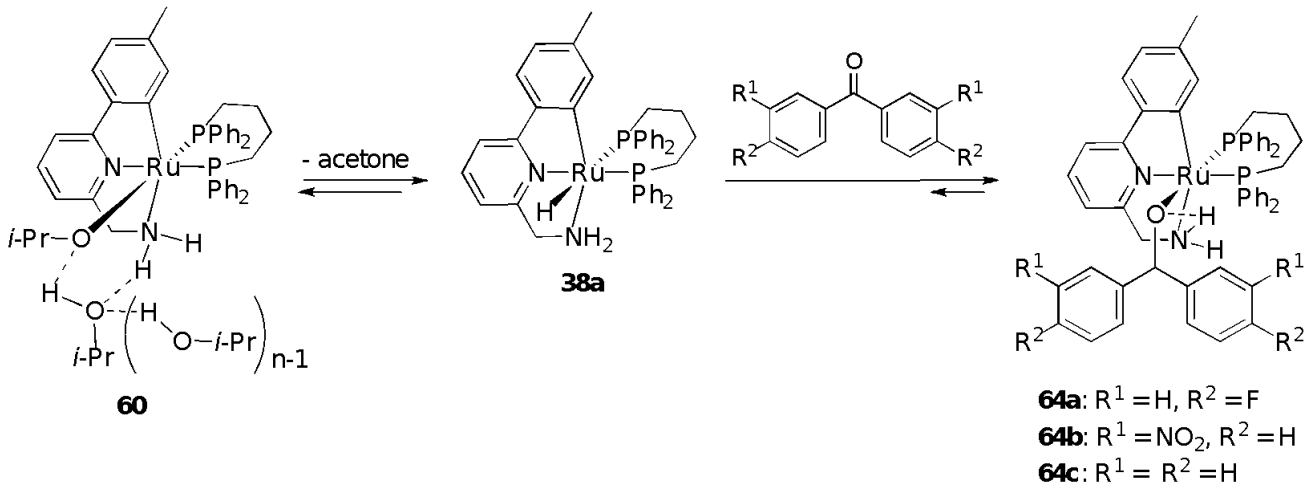
These investigantions suggest that both isopropoxide **60** and the hydride **38a** are involved the catalysis, while no Ru-amide intermediates could be detected in solution.



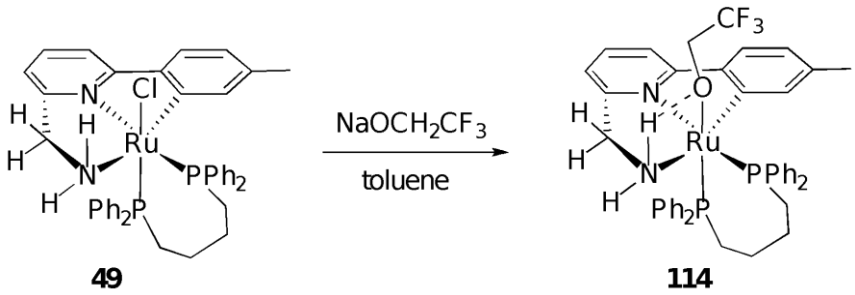
Scheme 73. Reversible β-hydrogen elimination from isopropoxide Ru-complexes.

Although the isopropoxide **37a** could not be isolated due to the presence of the fast equilibrium to the hydride **38a**, thermally stable alkoxides were obtained from ketones containing electron-withdrawing groups for which the β-hydrogen-elimination is hindered. Thus, the reaction of the isopropoxide **60** with bis(4-fluorophenyl)- or bis(3-nitrophenyl)methanone afforded the related alkoxide **64a** [52] or **64b** [38], respectively, via the hydride **38a**; while reaction of **38a** with benzophenone led to the alkoxide **64c** [32b] (Scheme 74).

The stability of these alkoxides vs **38a**/ketone was ascribed to the high redox potential of the related diaryl ketones compared to dialkyl ones [53], shifting the reaction toward the alkoxides. A clear-cut evidence accounting for the stability of these species has been provided by the alkoxide **114**, prepared in 93% yield by treatment of **36a** with $NaOCH_2CF_3$ stabilized through an intramolecular O···H–N hydrogen bonding inferred from NMR spectroscopic and neutron diffraction studies (Scheme 75) [54].

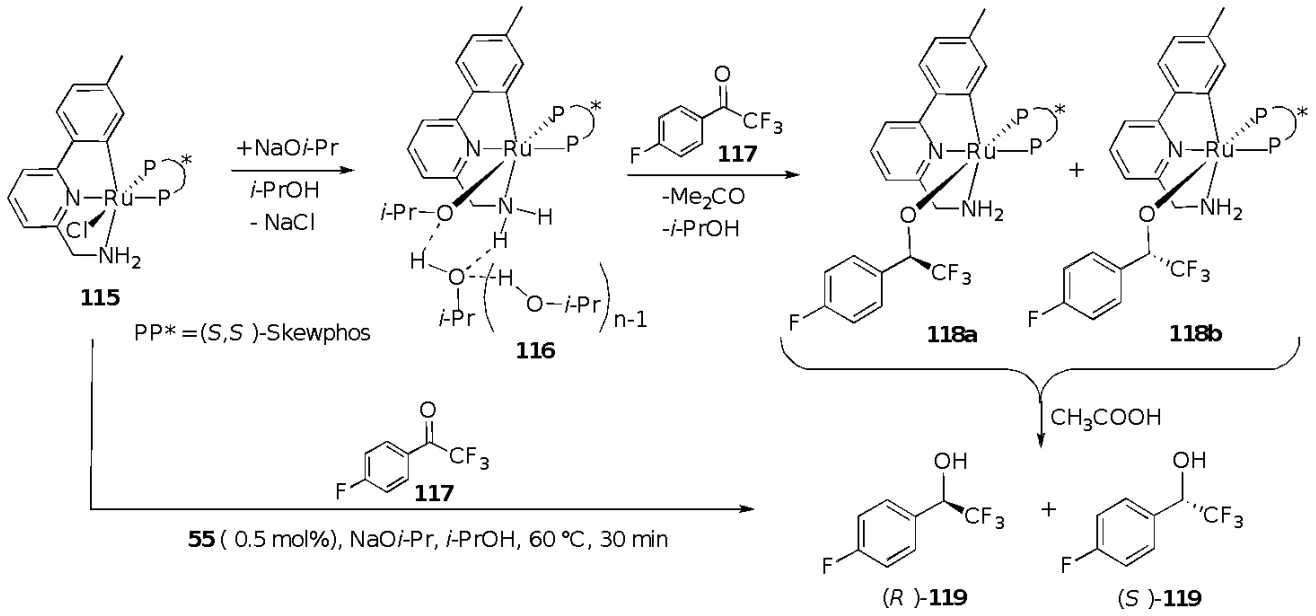


Scheme 74. Synthesis of the alkoxides **64a**,**c**.



Scheme 75. Synthesis of the alkoxide **114**.

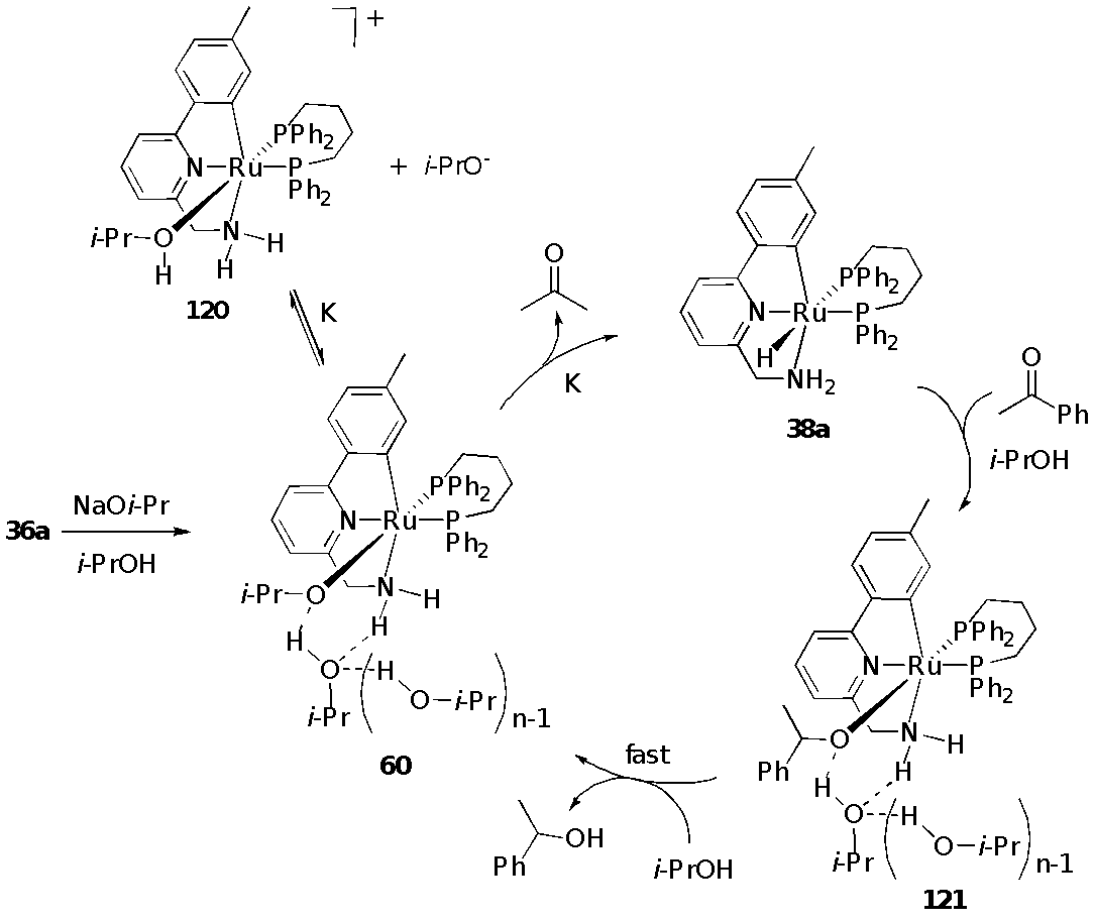
Further evidence of the involvement of alkoxide ruthenium species in the TH was given by catalytic and stoichiometric reduction of the prochiral ketone 2,2,2-trifluoro-1-(4-fluorophenyl)ethanone (**117**) involving the chiral CNN complex **115** prepared from $RuCl_2(PPh_3)_3$, the diphosphine (*S*,*S*)-Skewphos) and the HCNN ligand (Scheme 76) [52]. When the alkoxide **116**, obtained from **115** and NaO*i*Pr in 2-propanol, was reacted with the ketone **117**, a mixture of the diastereomer alkoxides **118a** and **118b** in a 5:1 molar ratio (67% *de*) was obtained (74% yield) via Ru-hydride and elimination of acetone [52]. Protonation of this mixture with acetic acid afforded (*R*)- and (*S*)-2,2,2-trifluoro-1-(4-fluorophenyl)ethanol (*R*)- and (*S*)-**119**, respectively, with the *R* enatiomer prevailing (66% ee). Since the same stereoselectivity (64% ee) was obtained in the reduction of the ketone **115** with catalyst **117** under standard TH conditions, there were strong indicatations that diastereomeric ruthenium–alkoxides are species involved in the catalytic ATH of ketones promoted by Ru-NH_2 systems.



Scheme 76. Formation of the diastereomeric alkoxide Ru-complexes **117**,**118** and related alcohols.

Kinetic studies on the catalytic TH of acetophenone suggested that the isopropoxide **60**, formed by reaction of **36a** with NaO*i*-Pr in 2-propanol, rapidly equilibrates with the cationic alcohol adduct **120** (catalyst reservoir) with a pre-equilibrium constant of about $K \sim 2 \times 10^{-5}$ M (Scheme 77) [55]. Complex **60** undergoes a β-hydrogen elimination affording the hydride **38a** that reacts with acetophenone, leading to the alcohol-adduct alkoxide **121**. In the final step this species rapidly reacts with 2-propanol (in excess), affording 1-phenylethanol and **60** that closes the cycle. The formation of **38a** from **60** is likely to be rate determining step of the catalytic TH, in which **60** is the predominant species. The activation parameters ($\Delta H^{\#} = 14.0 \pm 0.2$ kca-mol^{-1} and $\Delta S^{\#} = -3.2 \pm 0.5$ eu) suggested that no substantial rearrangement occurs in the rate determining step. This is in agreement with an intramolecular conversion of alcohol adduct alkoxide **60** into the hydride **38a**, through a cleavage of the C-H bond within a hydrogen bonding network promoted by the Ru-NH_2 functionality.

Eliminare i-PrOH sopra la doppia frecca di equilibrio, cioè dove c'è K



Scheme 77. Catalytic cycle for TH of acetophenone by the Ru-complex **36a**.

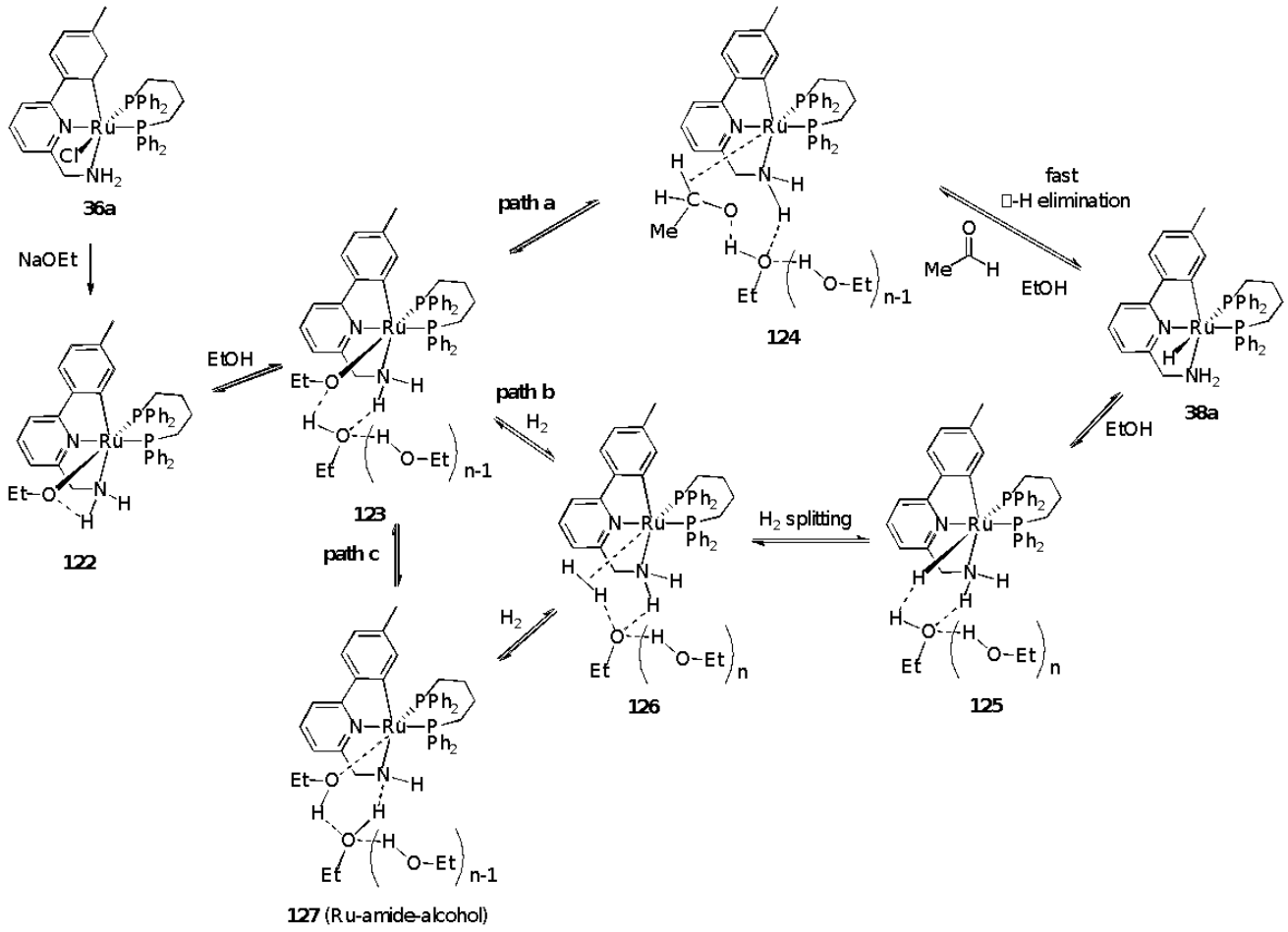
While the ketone TH occurs in 2-propanol, catalytic studies on the HY of carbonyl compounds promoted by **36a** showed that the alcohol media plays an important role, ethanol showing better performance compared to 2-propanol or methanol. NMR investigations carried out on the species that form when **36a** is reacted with NaOEt/EtOH mixtures revealed the presence of several species in equilibrium, involving the alcohol and the NH function (Scheme 78).

Treatment of the chloride precursor **36a** with NaOEt in [D_6]benzene leads to the ethoxide **122**. Addition of EtOH (3 equiv) produces the alcohol adduct **123** (**122**/**123** = 1:3), which equilibrates with the hydride **38a** (**38a**/**123** = 3:4) at 25 °C [54]. When a greater amount of EtOH (10 equiv) is used, compound **123** is obtained through solvation of **122** and protonation of **38a** with concomitant formation of H_2 (**38a**/**123** = 1:7). By using 25 equiv of EtOH, compounds **122** and **38a** are converted almost quantitatively to **123** (>95%). When a solution of **123** containing 25 equiv of EtOH is kept under H_2 (5 atm), the hydride **38a**, which is present in trace, starts to form through hydrogen splitting, affording a mixture **38a**/**123** in 2:3 ratio.

Catalytic investigations on the HY of acetophenone with **36a** in ethanol show that high activity is observed in a defined “pH window” [54]. As a matter of fact, under acidic conditions the Ru-H would

be protonated resulting in H_2 formation, whereas in basic conditions the presence of a large amount of alkoxide may prevent H_2 coordination to the Ru center. By contrast, the rate of the catalytic TH of acetophenone in 2-propanol increases with the alkoxide concentration, reaching a *plateau* [55].

These studies showed that the NH_2 function of the pincer complexes stabilizes the alkoxide complexes both through intramolecular hydrogen bond interactions involving the N–H parallel to the OR ligand, and through hydrogen bonds with the external alcohol. In addition, this hydrogen bonding network leads to highly labile alkoxide complexes, which easily convert to the hydride species. The catalytically active hydride **38a** can be formed from the Ru-alkoxide through two pathways: (1) a fast β–hydrogen-elimination (path a, Scheme 78) and (2) a slower dihydrogen splitting (path b). As an alternative to path b, complex **123** could be in equilibrium with the Ru-amide-alcohol adduct (path c, Scheme 78).



Scheme 78. Formation of the hydride **38a** from the alcohol-adduct ethoxide **123** through reversible β-hydrogen elimination and heterolytic dihydrogen splitting.

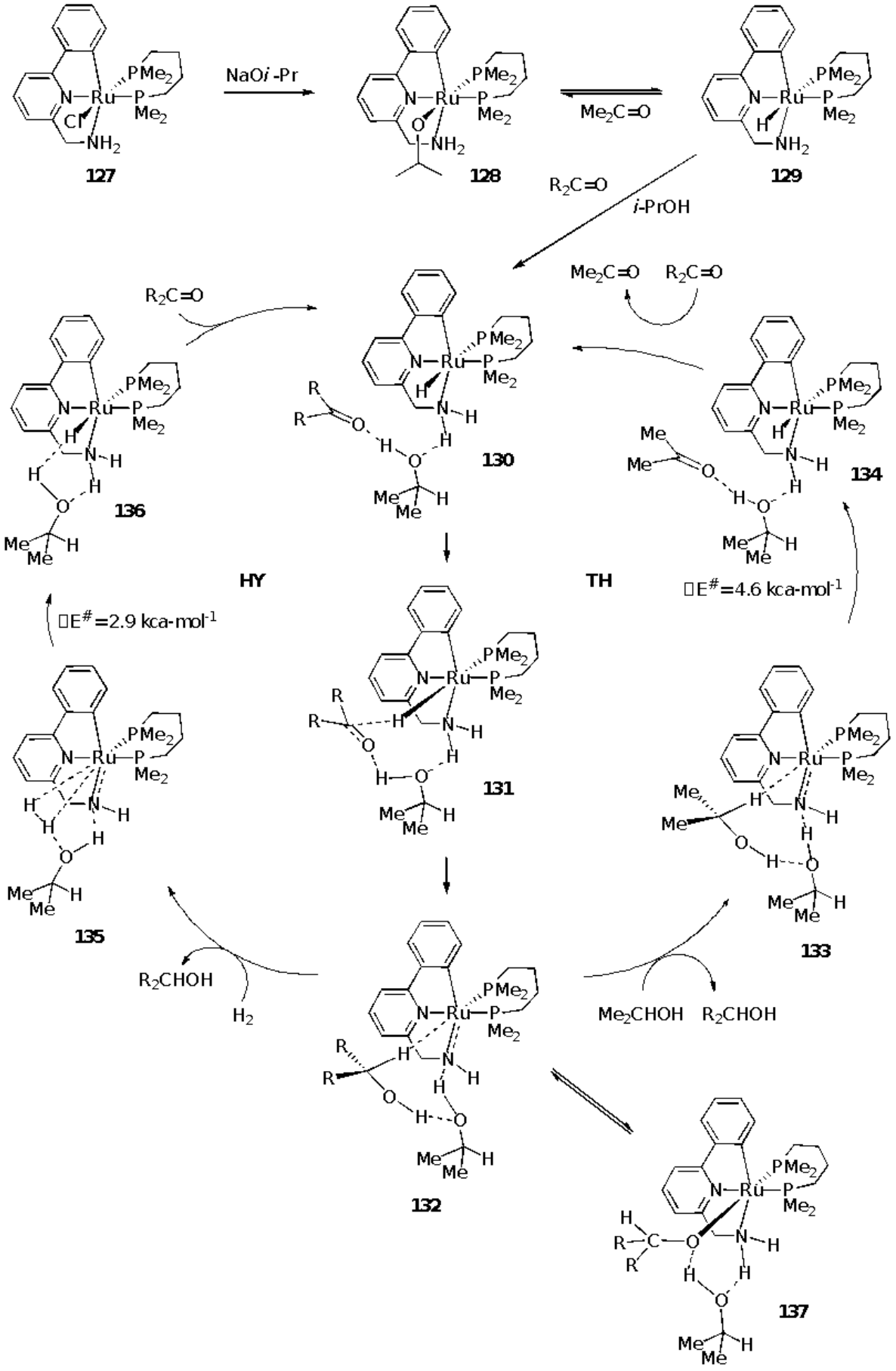
Eliminare spazio

The detection of the alkoxide and hydride species led us to investigate the energetic profile of the species involved in the catalytic cycle, in which the NH_2 function and the alcohol media play such a crucial role. Even if the expected amido intermediate was not detected in solution, the possibility of its formation in the catalysis could not be excluded, as supported by theoretical calculations.

Density functional theory (DFT) calculations carried out on model complexes RuX(CNN)(dmpb) (X = H, OR) (HCNN = 2-aminomethyl-6-(phenyl)pyridine, dmpb = $Me_2P(CH_2)_4PMe_2$) in the presence of added molecule of 2-propanol showed that the reaction of the Ru hydride with the ketone substrate leads to the most stable Ru alkoxide, the species observed in solution by NMR [54].

According to these calculations, the hydride **129**, obtained from **127** via the isopropoxide **128**, reacts with the substrate ketone in the presence of 2-propanol affording the intermediate **130** (Scheme 79). Both TH and HY processes occur via reduction of the ketone in **130**.

The regeneration of the catalytic active hydride species may occur via two routes, namely via TH by displacement of the alcohol product R_2CHOH with 2-propanol (right cycle) or via HY by substitution of R_2CHOH with H_2 (left cycle). The differences of the energy barriers between the two processes are very small. TH is limited by the C-H activation ($\Delta E^{\#} = 4.6$ kca-mol^{-1}), whereas HY is controlled by H_2 activation ($\Delta E^{\#} = 2.9$ kca-mol^{-1}), leading in both cases to the hydride complex. Notably, under the catalytic conditions, the Ru alkoxides are the predominant species, which quickly equilibrate to the hydride and the other catalytic intermediates. The energy differences between the intermediate species connected by the transition states are very small, in agreement with the high catalytic activity of this system.



Scheme 79. Catalytic cycle for TH and HY of carbonyl compounds with RuCl(CNN)(dmpb) (**127**) (CNN = 2-aminomethyl-6-(phenyl)pyridine) in the presence of 2-propanol as the solvent.

5. Hydrogenation by molecular hydrogen of esters to alcohols

The hydrido carbonyl chlorides Os- and Ru-complexes **138** and **140** (Fig. 11) were prepared by treatment of the $MHCl(CO)(AsPh_3)_3$ (M = Os, Ru) precursors with the ligand $PyCH_2NHC_2H_4P$*i*-Pr_2 [56]. Treatment of these complexes with KO*t*-Bu afforded the unusual dimers **139** and **141** (Fig. 11). The catalytic activity of the complexes **138**–**141** under H_2 (50 bar) was first tested in the HY of methyl benzoate to give benzyl alcohol and MeOH. The ultimate performance was observed with the Ru-dimer **141**, which gave 18.000 turnovers in 17 hours at 100 °C by using 0.005 mol% of the catalyst without base. Os-dimer **139** was also an efficient catalyst, displaying a slower rate compared to **141**. The chlorides **138** and **140** were similarly active in the presence of KO*t*-Bu. The complexes **139**,**141** were further investigated in the HY of several esters (Scheme 80) and representative alkenoates (Scheme 81) at 100 °C under 50 bar H_2. The Os-catalyst **139** was equally active for the HY of ethyl, *i*-butyl benzoates and ε-caprolactone, but failed with isopropyl 2-bromobenzoate and methyloxalate (Scheme 80). Activity and selectivity of the complexes **139**–**141** were tested with substrates containing C=C bonds. The results showed significant differences for Ru- and Os-complexes (Scheme 81). Hydrogenation of methyl 2-nonenoate was not selective with **139** and **140** affording methyl nonanoate and nonanol, respectively. Os-dimer **139** successfully catalyzed reduction of methyl 3-nonenoate to 3-nonenol, whereas Ru-dimer **141** proved inactive in this reaction. Methyl oleate was hydrogenated with **139** with retention of the C=C bond to give (Z)-octadec-9-enol. The same reaction was very sluggish and required more catalyst with **141**; the reaction also lacked selectivity and afforded a mixture of octadecanol and (*E*)- and (*Z*)-octadec-9-enols.

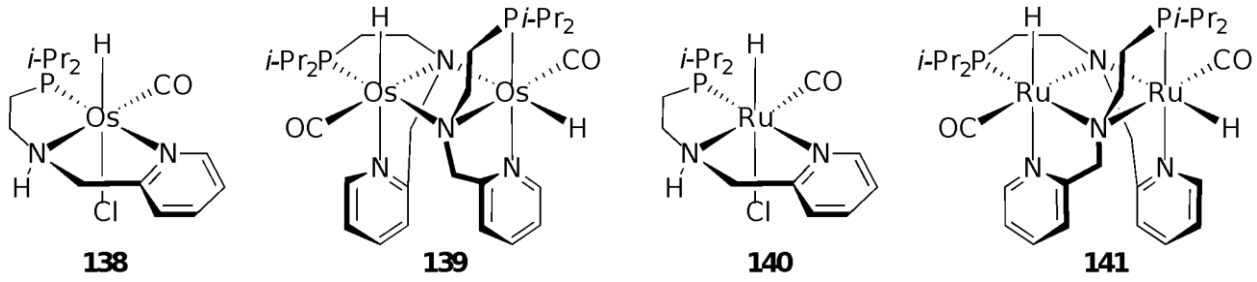
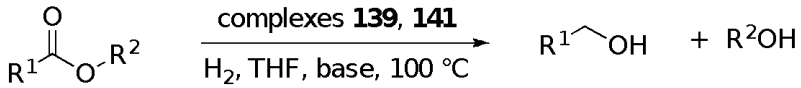


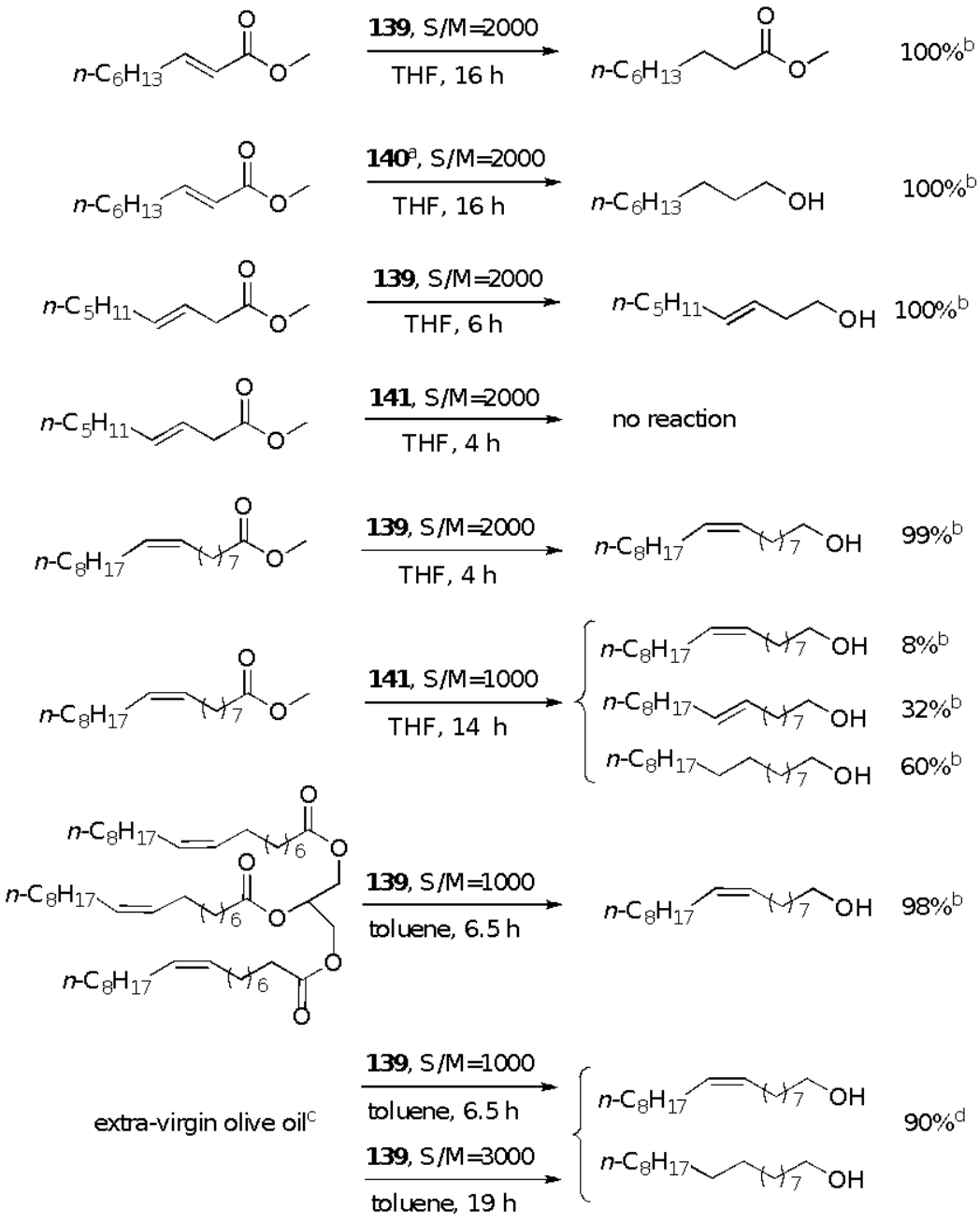
Fig. 11. Chemical structure of the Os- and Ru-complexes **138**-**141**.



R^1	R^2	complex	time (h)	conversion (%)
Ph	Et	**139**	1.6	99
Ph	*i*-Bu	**139**	1.5	93
2-BrC_6H_5	*i*-Pr	**139**	17	0
n-C_5H_{11}	Me	**139**	2	100
Me	Et	**139**	3	100
-$(CH_2)_5$-		**139**	1.4	99
-$(CH_2)_5$-		**141**	5	67
MeCH(OH)	Me	**139**	9	72
MeOC(O)	Me	**139**	23	0
MeO	Me	**141**	5.7	85

Reaction conditions: substrate (20 mmol), molar ratio substrate/metal = 2000, H_2 (50 bar), THF (7 mL) at 100 °C.

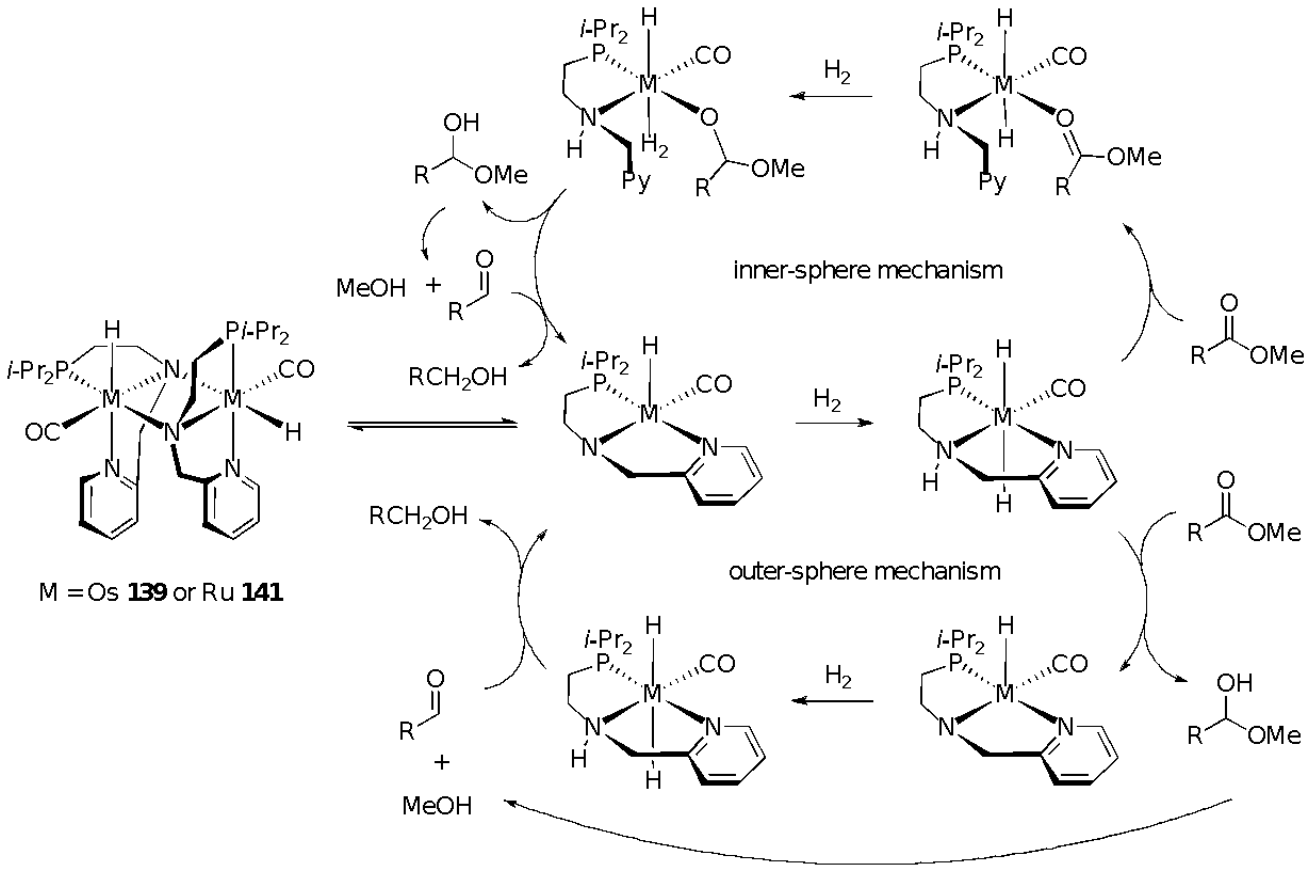
Scheme 80. HY of esters catalyzed by the Os- and Ru-complexes **139** and **141**.



Hydrogenation of alkenoates at 100 °C and H_2 (50 bar), S/M = molar ratio of alkenoate groups to metal. [a]With *t*-BuOK (0.5 mol%). [b]Conversion. [c]A mixture of triglycerides of oleic (ca. 85%), linoleic (ca. 2–3%), and palmitic acids as the main components. [d]Total yield of isolated alcohol mixture, containing approximately 85% of oleyl alcohol.

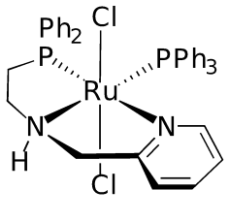
Scheme 81. HY of alkenoates catalyzed by the Os- and Ru-complexes **139**,**140** and **141**.

The authors indicated that both the Noyori-type outer-sphere and the classical innersphere hydrogenation mechanisms were possible with the NNHP*i*-Pr complexes (Scheme 82). The superior activity of **139** versus $RuH_2(CO)(HN(C_2H_4P\textit{i}\text{-}Pr_2)_2)$ [57] for HY of methylbenzoate suggested an important role of hemilability of the NNHP*i*-Pr-coordinated catalysts.



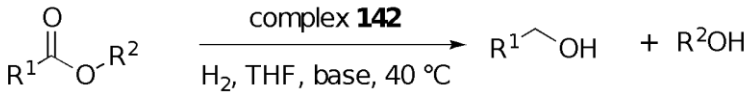
Scheme 82. Inner- and outer-phere mechanism for ester hydogenation catalyzed by complexes **139** or **141**.

Next, Gusev and Spasyuk demonstrated that the Ru-complex **142** (Fig. 12) is an outstanding versatile catalyst for different processes [58]. With this complex a number of esters were converted into the related alcohols in high yields under 50 bar H_2 at 40 °C, giving an unprecedented 20.000 turnovers in 16 h for ethyl acetate and 18.800 turnovers in 18 h for methyl hexanoate (Scheme 83).



142

Fig. 12. Chemical structure of the Ru-complex **142**.



R^1	R^2	complex[a]	base (mol%)	time (h)	yield (%)
Ph	Me	0.025	KOMe (5)	16	98
Me	Et	0.005	NaOEt (1)	16	100
n-C_5H_{11}	Me	0.005	KOMe (5)	18	94
$MeOCH_2$	Me	0.025	KO*t*-Bu (1)	16	100
MeCH(OH)	Me	0.05	KOMe (10)	16	98

Reaction conditions: H_2 (50 bar) at 40 °C. [a]Complex (mol%).

Scheme 83. HY of esters catalyzed by the Ru-complex **142**.

The same group has vere recently reported the hydrogenation of esters by the Os-complexes **106a**,**c**-**108**,**111** and Ru-complex **109** (Fig. 8 and Scheme 69) [48]. Among them, the complex **106b** resulted to be the most performing catalyst. The hydrogenation results obtained by **106b** under 50 bar H_2 at 100 °C are organized in Scheme 84. Among the substrates, the non-conjugated compounds that are not base-sensitive (**E1, E2**, **E5**, **E9**, Fig. 13) were most efficiently hydrogenated in the presence of 1–2% NaOMe, preferably without solvent. Moderately base-sensitive compounds that react with metal alkoxides (**E4**, **E6**, **E7**, **E8**, Fig. 13) were selectively reduced in the presence of a carbonate base, optionally neat or in 2-propanol. The use of 0.2 mol% K_2CO_3 in 2-propanol was particularly recommended. Selective catalytic hydrogenation of α,β-unsaturated esters (**E10**–**13**, Fig. 13) remained an elusive target. Also the dihydride **111** resulted a efficient catalyst for the hydrogenation of neat esters at room temperature, under 50 bar H_2 without base. For instance, 0.01 mol% **111** in methylformate gave methanol in 1 h (TOF = 1570 h^{-1}). HY of neat methylacetate, ethylacetate, and ethylbutyrate with 0.05 mol% **111** afforded the corresponding alcohols with TOF = 730, 715, and 530 h^{-1}, respectively. HY of ethyl acetate with **111** and 1 mol% NaOMe gave ethanol (TOF = 740 h^{-1}), while an experiment without base at 40 °C increased the rate (TOF to 1.315 h^{-1}). None of the above reactions produced NMR-observable aldehyde or hemiacetal intermediates.

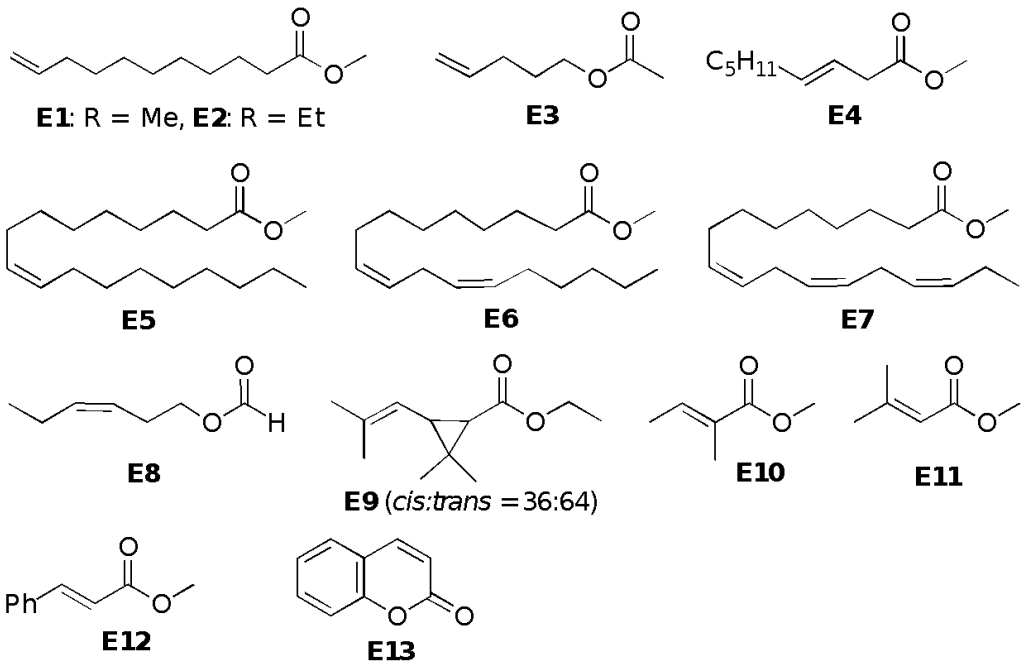
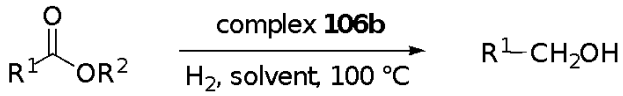


Fig. 13. Esters used in the HY by the Os-complex **106b**.



s[a]	complex[b]	time (h)	solvent	base[c]	sel (%)[d]	conv (%)[e]
E1	0.01	5	neat	NaOMe, 2	98	98
E2	0.01	4	neat	NaOMe, 2	96	97
E3	0.05	2	*i*-PrOH	K_2CO_3, 0.2	98	100
E4	0.05	2	*i*-PrOH	K_2CO_3, 0.2	99	99
E5	0.01	4	neat	NaOMe, 2	100	98
E6	0.05	3	neat	Cs_2CO_3, 1.5	100	98
E7	0.05	3	neat	Cs_2CO_3, 1.5	100	98
E8	0.02	2	*i*-PrOH	K_2CO_3, 0.2	100	>99
E9	0.05	24	neat	NaOMe, 2	100	98[f]
E10	0.05	1.5	*i*-PrOH	Cs_2CO_3, 0.2	0	57
E11	0.05	2	MePh	Cs_2CO_3, 1.5	0	61
E12	0.02	2	*i*-PrOH	K_2CO_3, 0.2	0	98
E13	0.02	2	*i*-PrOH	K_2CO_3, 0.2	0	100

Reaction conditions: H_2 (50 bar) at 100 °C. [a]Substrate. [b]Complex, mol%. [c]Base, mol%. [d]Selectivity (100%) when no C=C hydrogenation). [e]Total (saturated + unsaturated) % conversion to alcohol. [f]*Cis:trans* = 37:63.

Scheme 84. HY of the esters **E1**–**E13** (Fig. 13) catalyzed by the Os-complex **106b**.

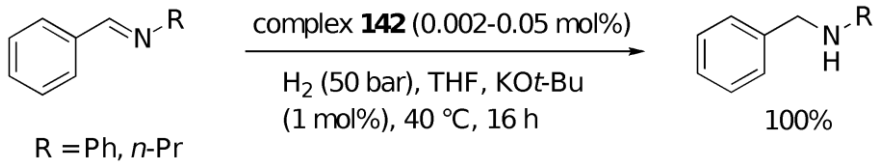
6. Hydrogenation by molecular hydrogen of imines

We have demonstrated that the Ru-complex **50** (Scheme 30) is also an active catalyst for the reduction of imines [47]. In particular, *N*-benzylaniline was hydrogenated under 5 atm H_2 at 40 °C

(imine/**50**/KO*t*-Bu = 5000:1:100), giving *N*-benzylaniline in 93% conversion after 10 h, but with a significantly lower rate (TOF = 1.4 x 10^3 h^{-1}) relative to that of carbonyl substrates, which are characterized by a stronger polarity of the C=X bond.

Eliminare spazio

Gusev and Spasyuk demonstrated that the Ru-complex **142** is also an efficient imine hydrogenation catalyst, giving a particularly high TON = 50.000 for *N*-benzylaniline under 50 bar H_2 at 40 °C (Scheme 85) [57].



Scheme 85. HY of imines catalyzed by the Ru-complex **142**.

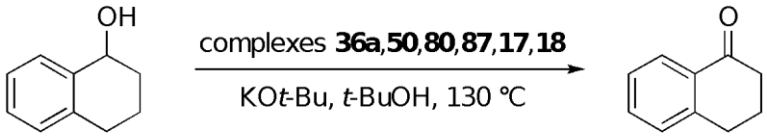
7. Dehydrogenation of alcohols to ketones

Catalytic alcohol dehydrogenation, through the direct formation of hydrogen and without the need of oxidizing agents, is a straightforward route to achieve carbonyl compounds, such as ketones, aldehydes, and esters [59]. A number of transition-metal complexes have been shown to display good to high catalytic activity for both H_2 generation and the preparation of carbonyl compounds from alcohols, ruthenium being the metal of choice.

In this contest, we have recently reported the use of a variety of pincer and diamine Ru and Os diphosphine complexes in the dehydrogenation of alcohols to ketones [19]. This was the first example of the use of Os complexes in this process. Among the examined complexes there are the pincer Ru- and Os-complexes **36a** (Scheme 21), **50** (Scheme 30), **80** (Scheme 46) and **87** (Scheme 50), and the Ampy derivatives **17** and **18** (Scheme 10).

The Ru- and Os-complexes **36a** **50**,**80**,**87**,**17** and **18** catalyzed the dehydrogenation of 1,2,3,4-tetrahydro-1-naphthol (α-tetralol), which was taken as model compound on account of its low redox potential (E° = 0.080 V) [53]. High conversion of α-tetralol into α-tetralone (93 and 90%) was observed with the Ru-derivatives **36a** and **50** (0.4 mol%) and KO*t*-Bu (2 mol%) in *t*-BuOH at 130 °C within 24 h (Scheme 86). On the other hand the corresponding pincer Os-complexes **80** and **87** displayed lower activity, thus leading to incomplete formation of α-tetralone (44 and 36%). The dppf derivative **17** and **18** with the Ampy ligand showed higher activity than the other complexes, affording 97 and 90% conversion after 4 h. It is noteworthy that the *cis*-isomer **18** showed a slightly lower activity with respect to the *trans*-isomer **17**, thus differing from the activity of $RuCl_2$(dppb)(Ampy) in the TH of ketones, for which the *cis*-isomers gave the highest rate [17].

Ultima riga invertire 90 con 4 cioè: **18** 4 90

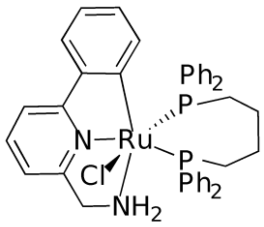


complex	time (h)	conversion (%)
36a	24	93
50	24	90
80	24	44
87	24	36
17	4	97
18	4	90

Reaction conditions: complex (0.4 mol%), KO*t*-Bu (2 mol%) in *t*-BuOH at 130 °C.

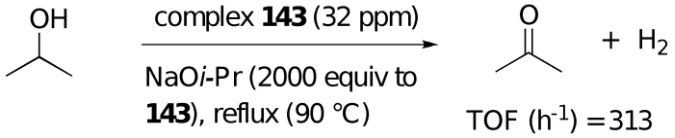
Scheme 86. Dehydrogenation of α-tetralol catalyzed by the complexes **36a**,**50**,**80**,**87**, **17** and **18**.

Beller and co-workers developed an efficient catalytic alcohol acceptorless dehydrogenation that employs mild, neutral reaction conditions [60]. Among the examined ruthenium and iridium catalysts there is the pincer complex **143 (**Fig. 14), which showed a decent activity in the dehydrogenation of 2-propanol to acetone, but at a lower level than that the other assessed complexes (Scheme 87).



143

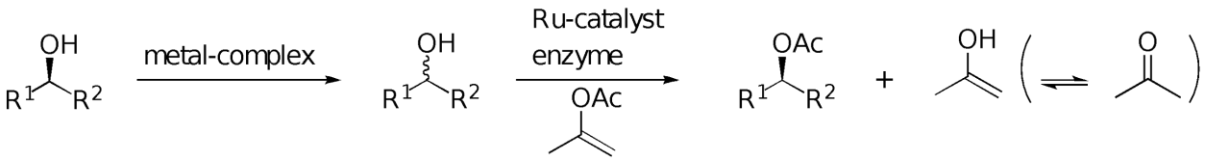
Fig. 14. Chemical structure of the Ru-complex **143**.



Scheme 87. Acceptorless dehydrogenation of 2-propanol to acetone catalyzed by the complex **143**.

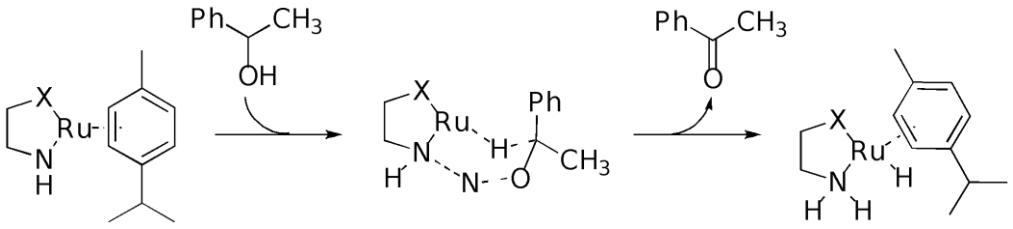
8. Racemization and deuteration of alcohols and amines

Chiral alcohols can be catalytically converted to racemates by several transition-metal complexes. This transformation is particularly relevant for dynamic kinetic resolution (DKR) in which a lipase is combined with a Ru-catalyst for the preparation of chiral alcohols (Scheme 88) [61].



Scheme 88. Racemization and dynamic kinetic resolution (DKR).

It is expected that highly active catalysts for TH of carbonyl compounds can also induce the activation of the C–H bond geminal (vicinal) to the hydroxyl group under proper reaction conditions. The NH_2 moiety in Ru-complexes appeared to be essential in the catalytic cycle in TH of ketones [11b]. This effect was designated by Noyori as bifunctional molecular catalysis, and is related to the interconversion of an amido Ru-complex (16-electron) and an amine hydrido Ru-complex (18-electron) as denoted in Scheme 89. Since TH of ketones in 2-propanol is a reversible reaction, achiral catalysts can be employed in the racemisation of chiral alcohols. Arends and co-workers evaluated in the racemization process a series of $(RNH_2)Ru(\eta^6\text{-arene})$ complexes and the two ortho-ruthenated complexes **26** (Scheme 15) and **36a** (Scheme 24) featuring an 2-aminomethylpyridine (Ampy) motif [62].



Scheme 89. Outer-sphere mechanism for hydrogen transfer catalyzed by Ru-NH ligand complexes.

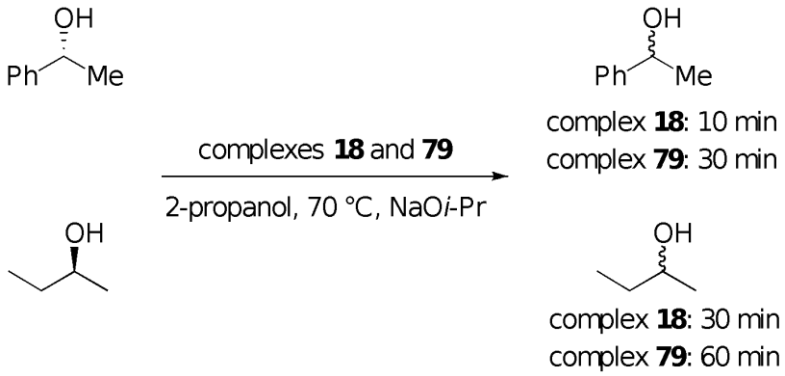
Complexes **26** and **36a** in toluene at 70 °C were inactive for the (*S*)-1-phenylethanol racemization, which on the other hand were efficient catalysts in the presence of *t*-BuOK. The role of the base is to generate a Ru-hydride species via displacement of the chloride ligand with alkoxides and β-hydrogen-elimination of acetophenone [63]. The complexes **26** and **36a** resulted among the fastest catalysts reported for racemization of secondary alcohols. Thus, at 70 °C full racemization of

(*S*)-1-phenylethanol occurred in 30 min by using 2 mol% of **26** and only 10 min by employing 1 mol% of **36a**.

Unfortunately, complexes **26** and **36a** resulted unsuitable for the DKR of 1-phenylethanol, since the true catalytic species derived from these precatalysts were deactivated in the presence of lipase and acyl donors . In an attempt to unravel the mechanism of deactivation of the Ru-hydride species presumably formed during the catalytic reaction, the hydride **38a** (Scheme 24) was isolated from the equilibrium arising from the reaction of **36a** with *i*-PrOK in *i*-PrOH at 60 °C. Upon extended reaction of **38a** with a ten-fold excess of isopropyl acetate a new single species was detected upon reaction completion. This formed species was proven to be inactive towards racemization of (*S*)-1-phenylethanol under DKR.

Eliminare spazio

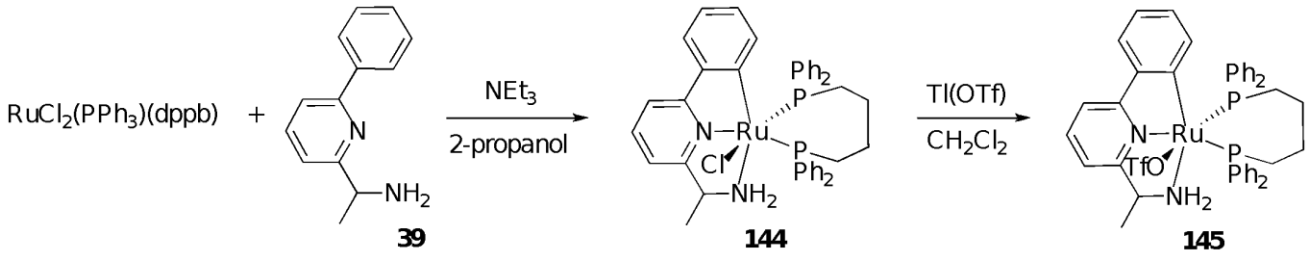
We have recently investigated on the racemization of chiral alcohols by the Ru- and Os-complexes **18** and **79**, respectively [18]. Reaction of (*R*)-1-phenylethanol (0.33 M) in 2-propanol at 70 °C with **18** (0.5 mol%) and in the presence of NaO*i*-Pr (2.0 mol%) led to complete racemization within 10 min (Scheme 90). Complex **79** was also catalytically active, affording the racemic alcohol in 30 min. The aliphatic alcohol (*S*)-2-butanol with **18** gave complete racemization in 30 min, whereas with **79** the reaction was slower, leading to the racemate in 1 h.



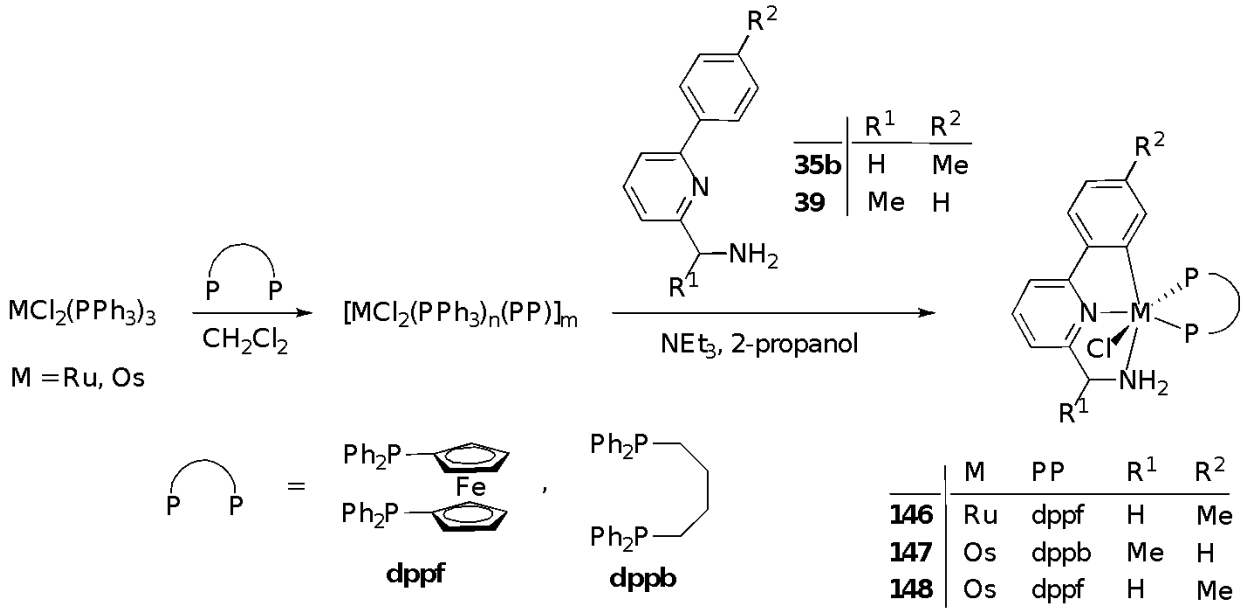
Scheme 90. Racemization of optically active alcohols catalyzed by Ru- and Os-complexes **18** and **79**.

Recently, we have found that the Ru- and Os-complexes **17**, **36a**,**79**,**80**,**81**,**144-148** in 2-propanol are efficient catalysts for the racemization of secondary alcohols [64]. These systems also efficiently catalyze the deuteration of primary and secondary alcohols in 2-propanol-d_8. The orthometalated Ru(II)-complex **144** 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 **39** in 2-propanol at reflux in the presence of NEt_3 in excess (Scheme 91). Treatment of **144** with one equivalent of thallium triflate in CH_2Cl_2 at room temperature (4 h) afforded the derivative **145** (Scheme 91). The pincer derivative **146**,

containing a rigid ferrocene diphosphine, was prepared by reaction of $[RuCl_2(PPh_3)_n(dppf)]_m$ with ligand **35b** in the presence of NEt_3 in refluxing 2-propanol. The intermediate $[RuCl_2(PPh_3)_n(dppf)]_m$ was obtained from $RuCl_2(PPh_3)_3$ with dppf in CH_2Cl_2 at room temperature (2 h) (Scheme 92). The Os-pincer **147**, analogous to the ruthenium **144**, was prepared by treatment of $OsCl_2(PPh_3)_3$ with dppb in CH_2Cl_2 at room temperature (3 h), followed by reaction with the ligand **39** and NEt_3 (10 equiv) in refluxing 2-propanol (3 h) (Scheme 92). Similarly, the ferrocenyl derivative **148** was obtained from $OsCl_2(PPh_3)_3$, dppf and ligand **35a** (Scheme 92).



Scheme 91. Synthesis of the Ru complexes **144** and **145**.



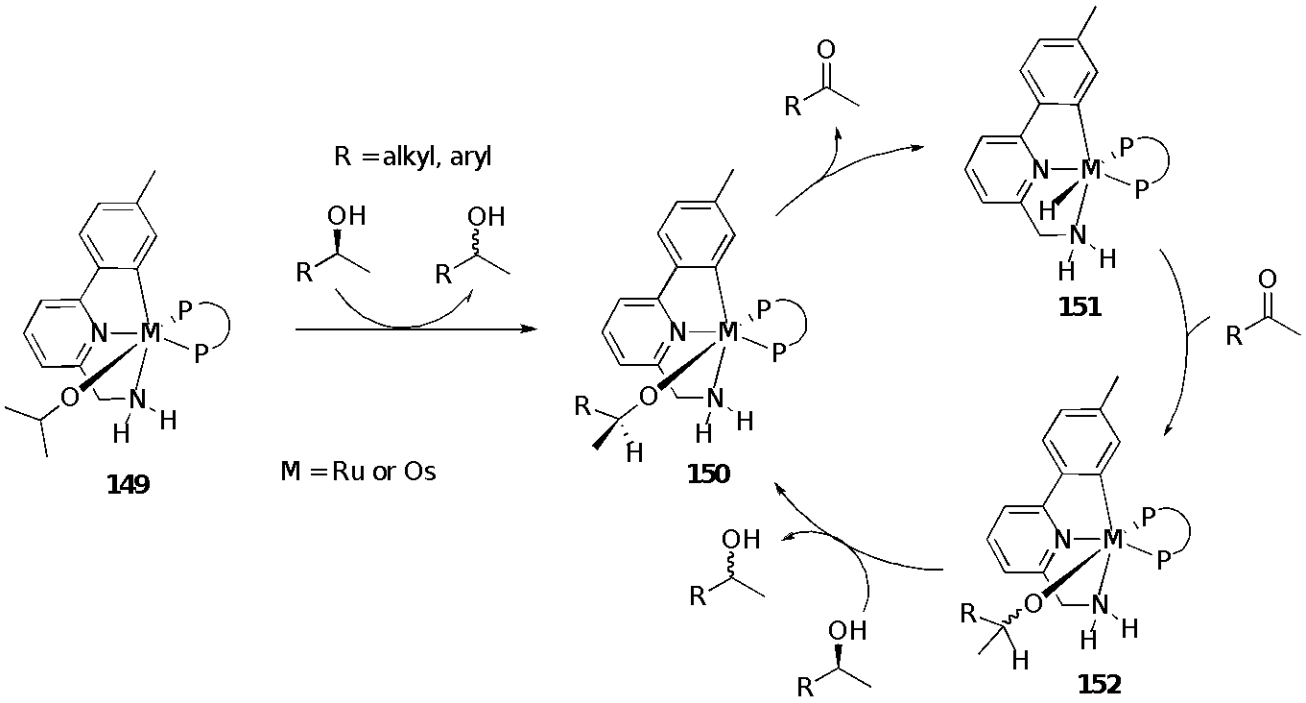
Scheme 92. Synthesis of the Ru- complex **146** and the Os- complexes **1476** and **1487** .

The pincer complexes ~~**144-148**,**36a**,**80**,**81**,**17 and 79**~~ **17**, **36a**,**79**,**80**,**81**,**144-148** (1 mol%) proved to efficiently catalyze the racemization of (*S*)-1-phenylethanol at 30–50 °C in the presence of KO*t*-Bu (5 mol%) in 2-propanol. The chiral aliphatic alcohols (*S*)-2-butanol and (*R*)-heptanol were also completely converted into the racemate in 2 h at 50 °C by complexes **36a**,**144**,**147**, whereas **148** showed moderate activity (64 and 48% *ee*, respectively, after 2 h). The racemization of (*S*)-1-phenylethanol was also carried out in non protic solvents, such as toluene, in the presence of a weak base. Complete

racemization occurred by complex **148** in the presence of DBU (10 mol%) at 90 °C after 6h. The comparison of the catalytic activity of the complexes $MCl_2(NN)(PP)$ (M = Ru, Os), bearing bidentate amine or pyridine ligands, showed that these systems are less active with respect to the pincer complexes. Thus, the *cis* Ampy Ru-complex **18**, which is related to **146**, is almost not active at 30 °C and affords racemization in 45 min at 90 °C. For osmium, the Ampy derivative **79**, which is related to the pincer **81**, affords 38% *ee* at 30 °C (2 h).

Eliminare spazio

In the proposed catalytic cycle for the alcohol racemization, the isopropoxide **149**, which is formed from MCl(CNN)(PP) in basic 2-propanol, is protonated by the chiral substrate alcohol leading to the alkoxide **150** (Scheme 93). This species affords the hydride **151** with extrusion of the ketone through a β-hydrogen elimination reaction, assisted by the NH_2 function and the 2-propanol media. The non-enantioselective reduction of the ketone affords **152**, which is protonated by the chiral alcohol, affording the racemic alcohol and closing the cycle.



Scheme 93. Proposed catalytic cycle for the racemization of alcohols catalyzed by Ru- and Os-pincer complexes in 2-propanol.

Primary and secondary alcohols were efficiently deuterated at the α-position, with respect to the OH group, in 2-propanol-d_8 as the solvent with Ru- or Os-pincer complexes in the presence of KO*t*-Bu at 30–50 °C. For secondary alcohols the 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

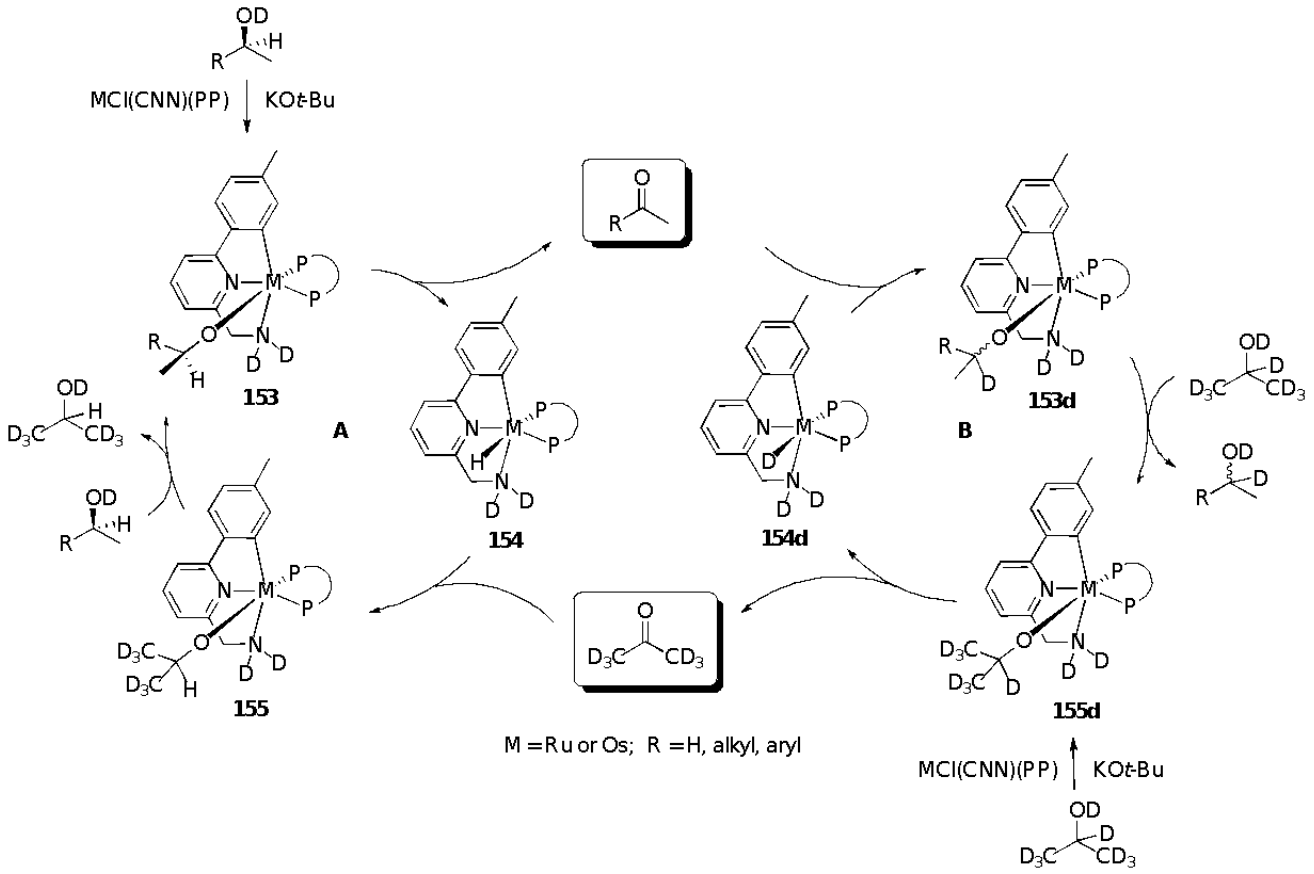
much the same activity was observed with the Ru and Os complexes. The pincer complexes display a superior activity with respect to the related compounds $MCl_2(NN)(PP)$ (M = Ru, Os; NN = bidentate amine or pyridine ligands).

Eliminare spazio

The catalytic pathway for the simultaneous deuteration and racemization of secondary alcohols, as well as the deuteration of the primary ones, may be envisioned as composed by two mirrored cycles, namely cycle **A** and cycle **B**, involving M–H and M–D species, respectively (Scheme 94) In the basic media, the precursor MCl(CNN)(PP) reacts with the alcohol substrate and also with 2-propanol-d_8 affording the alkoxides **153** and **155d** (respectively the upper left and lower right of Scheme 94), in which the NH_2 function of the pincer species is converted into the ND_2 moiety, due to the facile H/D exchange. According to the previous mechanism involving hydrogen elimination, complex **153** leads to the hydride **154** and the carbonyl compound, whereas **155d** gives the deuteride **154d** and acetone-d_6. The subsequent "cross" reactions of **154** with acetone-d_6 and **154d** with the carbonyl compound give the corresponding alkoxides **155** and **153d**. Finally, protonation of these species leads to 2-propanol-d_7 and the α-deuterated alcohol substrate, closing the cycles. 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.

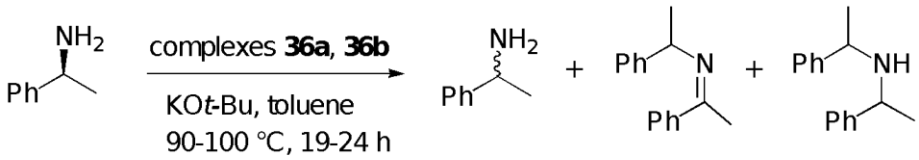
Eliminare spazio

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 ^1H 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 may be ascribed to the higher redox potential of the aldehydes compared to the ketones, affording a lower amount of free aldehyde *vs* ketone in solution.



Scheme 94. Proposed catalytic pathway for the racemization and deuteration of alcohols catalyzed by Ru and Os pincer complexes in 2-propanol-d_8.

Bäckvall group, developing a highly efficient protocol for DKR of amines, examined the Ru-complexes **36a** and **36b** (Scheme 21) in the racemization of (*S*)-1-phenylethylamine (Scheme 95) [65]. Complex **36a** showed very little activity for the racemization of this chiral amine, resulting in an enantiomeric excess value of 94%, whereas catalyst **36b**, which is the *N,N*-dimetylated derivate of **36a**, gave full racemization (0% ee) and high selectivity after 19 h at 100 °C. Unfortunately, catalyst **36b**, which is activated by KO*t*-Bu, proved to be ineffective in the DKR of amines



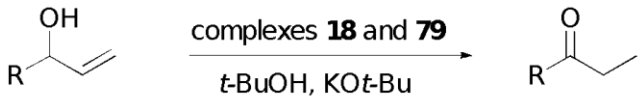
complex	temp (°C)	ee (%)	selectivity (%)[a]
36a[b]	90	94	>98
36b[c]	90	34	>98
36b[b]	100	0	>98

Reaction conditions: 1 mmol of (*S*)-phenylethylamine, 0.01 mmol of catalyst, 0.02 mmol of KO*t*-Bu, 1 mL of toluene, 24 h. [a]Selectivity for phenylethylamine. [b]19 h. [c]24 h.

Scheme 95. Racemization of (*S*)-1-phenylethylamine catalyzed by complexes **36a** and **-36b**.

9. Isomerization of allylic alcohols

The catalytic isomerization of allylic alcohols to ketones is an interesting route for the preparation of carbonyl compounds. Among the several transition-metal catalysts that have been developed for this transformation [66], a particular attention has been devoted to ruthenium, which led to the most active systems [67]. Recently, cyclopentadienyl Os-complexes with pendant amine ligands has been found to be active in the alcohol allylic isomerization [68]. We have recently showed that Ru- and Os-complexes **18** and **79** (1 mol%), with KO*t*-Bu (2 mol%) in *tert*-butyl alcohol catalyze the isomerization of monosubstituted aliphatic allylic alcohols with high selectivity (Scheme 96) [18]. The obtained data clearly indicated that Os-complex **79** display catalytic activity at higher temperature with respect to the Ru-complex **18**.



	complex **18**				complex **79**			
R	T (°C)	conv (%)	time (h)	TOF (h^{-1})	T (°C)	conv (%)	time (h)	TOF (h^{-1})
Me	70	94	10 min	6000	120	78	1	150
Et	70	93	30 min	480	120	90	30 min	300
n-Bu	70	94	30 min	440	120	85	1	460
Ph	120	93	2	160	120	62	3	150

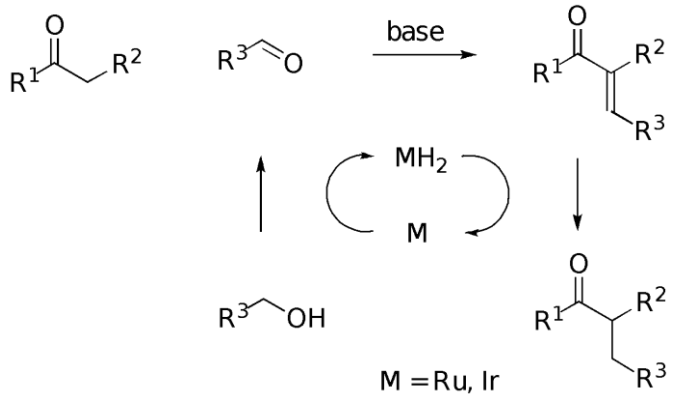
Reaction conditions: alcohol (0.33 M), complex (1 mol %) and KO*t*-Bu (2 mol %) in *t*-BuOH.

Scheme 96. Isomerization of allylic alcohols to ketones catalyzed by the Ru- and Os-complexes **18** and **79**.

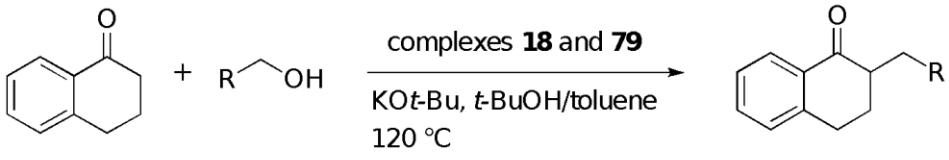
10. α-Alkylation of ketones

The α-alkylation of ketones using primary alcohols is an attractive step-economical synthesis that avoids the use of toxic alkylating reagents (e.g., organohalides). The Ru-complexes $RuCl_2(PPh_3)_3$ [69] and $Ru(DMSO)_4Cl_2$ [70] and the iridium system $Ir(COD)Cl]_2/PPh_3$ [71] have been described to catalyze this reaction. The transformation can be envisaged as a sequence of oxidation of alcohol/aldol condensation/reduction of the unsaturated ketone (Scheme 97) [59a].

The Ru- and Os-complexes **18** and **79** (0.5 mol%), efficiently catalyzed the alkylation of α-tetralone with several primary alcohols at 120 °C and in the presence of KO*t*-Bu (30 mol%) (Scheme 98) [18]. Apparently, no example of alkylation of ketones with simple alcohols (EtOH and *n*-PrOH) was previously described; most of the reactions involved the use of *n*-BuOH or $PhCH_2OH$ [59a]. The relatively low catalyst loading and the high rate indicated that **18** is an efficient system for this reaction, but surprisingly, the Os-derivative **79** displayed a higher activity compared to **18** (Scheme 98). Thus, the alkylation of α-tetralone with EtOH, *n*-PrOH, and *n*-BuOH was attained in 1 h, 30 min, and 10 min, respectively, with TOF up to 2.800 h^{-1}. No example of the use of Os in the α-alkylation of ketones was reported. The reduction of the unsaturated ketone intermediate may occur through hydrogenation at the C=C double bond or via reduction of the C=O bond, followed by isomerization of the allylic alcohol (Scheme 97).



Scheme 97. α-Alkylation of ketones by using primary alcohols.



	complex **18**			complex **79**		
R	conv (%)	time (h)	TOF (h^{-1})	conv (%)	time (h)	TOF (h^{-1})
Me	96	4	98	93	1	520
Et	87	2	230	91	30 min	910
n-Pr	92	3	420	93	10 min	2800

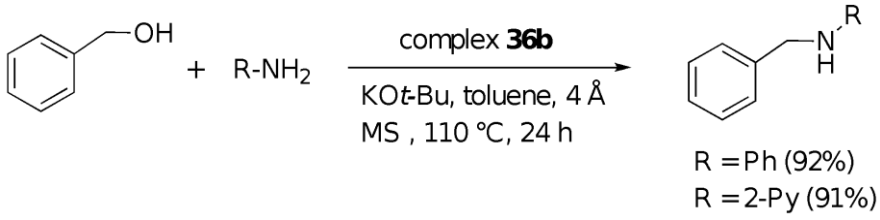
Reaction conditions: □-tetralone (0.33 M), alcohol (3 equiv), complex (0.5 mol%), KO*t*-Bu (30 mol%) in *t*-BuOH/toluene (1/2, v/v) at 120 °C.

Scheme 98. Alkylation of α-tetralone catalyzed by the Ru- and Os-complexes **18** and **79**.

11. *N*-Alkylation of amines

The principle governing the use of an alcohol as alkylating reagent involves its oxidation by a transition metal complex to a carbonyl compound, which after *in situ* reaction with an amine affords an imine; finally the formed imine is reduced by the transition metal hydride formed in the first step, yielding a higher order amine [72].

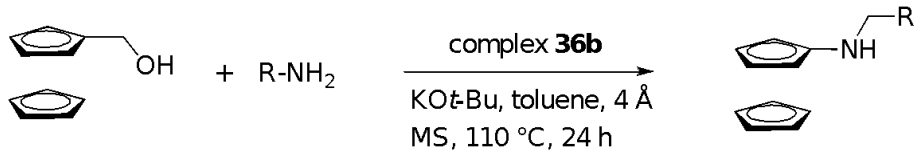
Martín-Matute and co-workers examined the Ru-complexes **36a,b** (Scheme 21) in the selective monoalkylation of amines with primary alcohols [73]. When benzyl alcohol and aniline or 2-aminopyridine were reacted in the presence of KO*t*-Bu, the complex **36b** catalyzed the formation of *N*-benzylaniline in excellent yield, while only moderate yield was obtained with **36a** (Scheme 99).



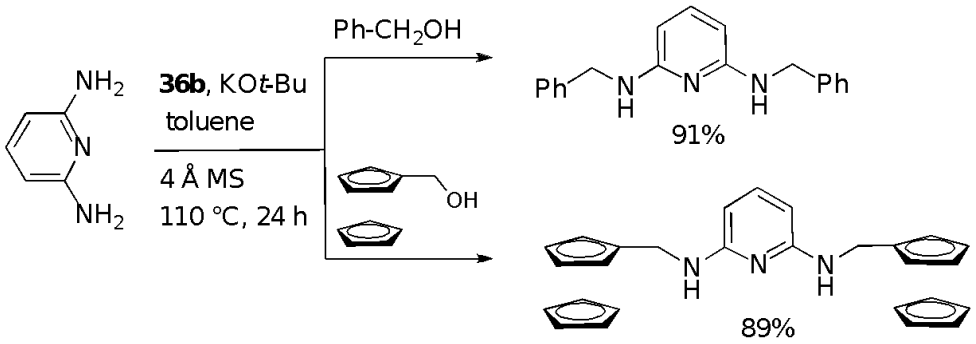
Scheme 99. Monoalkylation of amines with primary alcohols catalyzed by the Ru-complex **36b**.

Under optimal reaction conditions (toluene, KO*t*-Bu (1 equiv), molecular sieves 4 Å, 110 °C), ferrocenylmethanol reaccats with a number of substituted anilines, as well as 2-, 3- and 4-aminopyridines, affording secondary amines in good to excellent yields in the presence of **36b** (1 mol%) (Scheme 100). Also when 2,6-diaminopyridine was treated with either ferrocenyl- or phenylmethanol (2 equiv) the related diamines were formed in excellent yields (Scheme 100). The Ru-

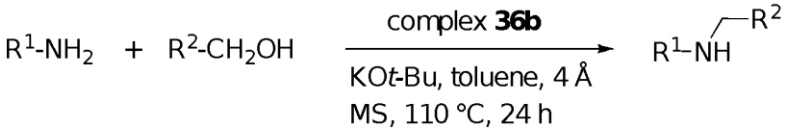
complex **36b** was highly active when heteroaromatic alcohols were used as alkylating reagents. Scheme 101 shows the results obtained in the *N*-alkylation of aniline and heteroaromatic amines by heteroaromatic alcohols affording *sec*-amines in good yields (71–86%). Since aliphatic amines were unreactive under the reaction conditions, aliphatic amino alcohols could be used as alkylating reagents. Thus, the reaction of aniline or 2-aminopyridine with three amino alcohols afforded the related *N*-arylated diamines in good yields (Scheme 102).



R =Ph (91%), 4-ClC$_6$H$_4$ (89%), 4-BrC$_6$H$_4$ (82%), 4-MeC$_6$H$_4$ (92%), 4-PhOC$_6$H$_4$ (91%), 2,5-Me$_2$C$_6$H$_3$ (90%), 2-Py (93%), 3-Py (90%), 4-Py (88%)



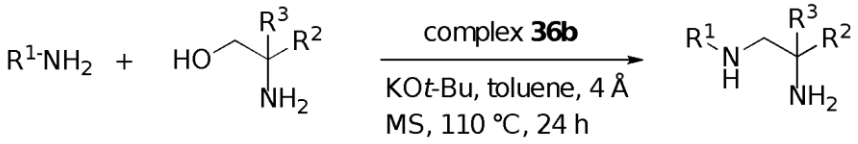
Scheme 100. Monoalkylation of amines with primary alcohols catalyzed by the Ru-complex **36b**.



R^1	R^2	yield (%)	R^1	R^2	yield (%)
Ph	2-furyl	86	2-py	2-furyl	81
Ph	2-thienyl	83	2-py	2-thienyl	81
Ph	2-pyridyl	74	2-py	2-pyridyl	71

Reaction conditions: complex (4 mg, 1 mo%), amine (0.5 mmol), alcohol (0.5 mmol), 4 Å MS , KO*t*-Bu (0.5 M in THF, 1 mL, 0.5 mmol) in dry toluene (0.5 mL), 24 h, 110 °C.

Scheme 101. Monoalkylation of amines with primary alcohols catalyzed by the Ru-complex **36b**.



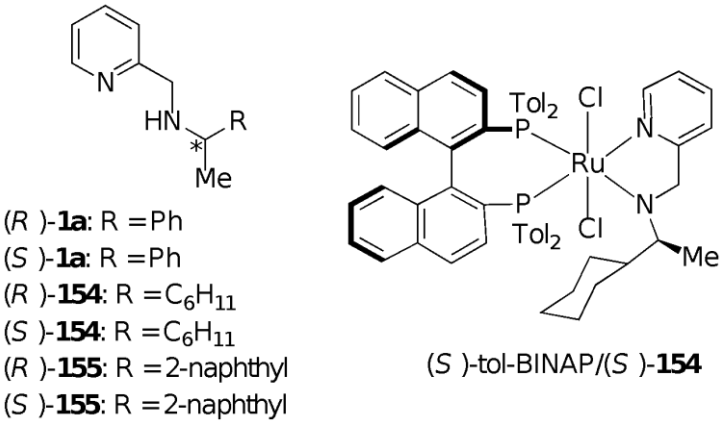
R^1	R^2	R^3	yield (%)	R^1	R^2	R^3	yield (%)
Ph	H	*i*-Pr	91	2-py	H	*i*-Pr	74
Ph	H	Et	83	2-py	H	Et	78
Ph	Me	Me	80	2-py	Me	Me	79

Reaction conditions: complex (4 mg, 1 mol%), amine (0.5 mmol), alcohol (0.5 mmol), MS 4 Å, KO*t*-Bu (0.5 M in THF, 1 mL, 0.5 mmol) in dry toluene (0.5 mL), 24 h, 110 °C.

Scheme 102. Monoalkylation of amines with aliphatic amino alcohols catalyzed by the Ru-complex **36b**.

12. Hydrosilylation of ketones

The asymmetric metal-catalyzed addidtion of Si-H bonds across the carbonyl group of ketones, followed by hydrolysis is an important way to obtain chiral secondary alcohols [74]. In this contest, in 1999 Murrer and co-workers published a study to identify mixed-ligand Ru-complexes that could be effective precatalysts for the asymmetric hydrosilylation of ketones [75]. The complexes were prepared by sequential treatment of $[RuCl_2(C_6H_6)]_2$ with (*S*)-tol-BINAP an then with a series of nitrogen containing ligands. Among them, there are the enantiopure aminopyridines **1a**,**154** and **155** (Fig. 15). In the asymmetric hydrosilylation of acetophenone (THF, Ph_2SiH_2, rtRT), the highest enantioselectivity (63%) was observed with the combination of ligands (*S*)-tol-BINAP and (*S*)-**154** , whereas with (*S*)-tol-BINAP/(*R*)-**154** no stereoselectivity0% ee was attained, according to a matched-mismatched effect of the chiral ligands.



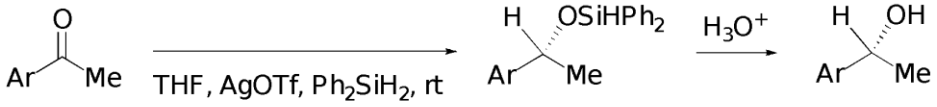
(*R*)-**1a**: R =Ph
(*S*)-**1a**: R =Ph
(*R*)-**154**: R =C_6H_{11}
(*S*)-**154**: R =C_6H_{11}
(*R*)-**155**: R =2-naphthyl
(*S*)-**155**: R =2-naphthyl

(*S*)-tol-BINAP/(*S*)-**154**

Fig. 15. Chemical structure of ligands **1a**,**154**,**155** and Ru-complex (*S*)-tol-BINAP/(*S*)-**154**

To confirm the validity of the results from parallel screening, the Ru-complex (*S*)-tol-BINAP/(*S*)-**154** (Fig. 16), giving the highest enantioselectivity, was isolated and assessed in the hydrosilylation of

acetophenone. The results obtained were consistent with the parallel experiments, the product alcohol being repeatedly obtained in 60–63% ee. Changing the reaction solvent had a detrimental effect on the enantioselectivity: MeCN (8% yield, 10% ee *R*), CCl_4 (11% yield, 12% ee *S*)), DME (92% yield, 12% ee *R*)), toluene (24% yield, 21% ee *R*). The addition of AgOTf, which generates coordination sites for binding the ketone and activating the Si-H bond, increased the enantioselectivity further to 82% ee. The optimised system proved to be effective for the hydrosilylation of different ketones (Scheme 103).

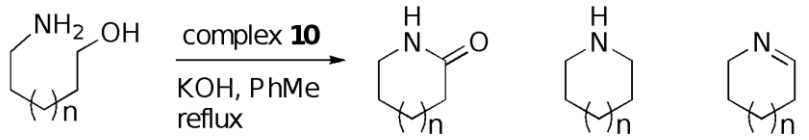


Ar	yield (%)	ee (%)
Ph	53	82
4-$MeOC_6H_4$	90	58
1-naphthyl	88	68

Scheme 103. Hydrosilylation of different ketones by the Ru-complex (*S*)-tol-BINAP/(*S*)-**154**.

13. Synthesis of amides from alcohols

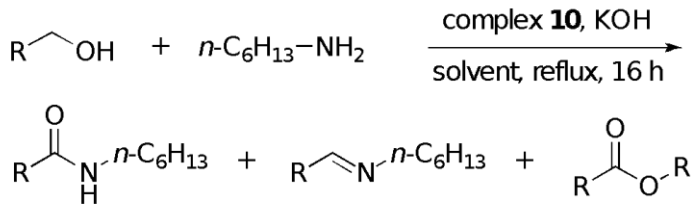
Crabtree and Eisenstein in a recent study highlighted some of the factors that are important in favoring the formation of amides vs alkylated amines in the Ru-catalyzed reaction of alcohols with amines [76]. For this study they used the Ru-complex **10** (Scheme 6) previously reported to have an exceptional TOF in standard catalytic TH [17]. It was found that complex **10** catalyzed the conversion of tree amino alcohols into lactams in the presence of KOH (other bases were assessed, but KOH provided the highest amount of amide in the product distribution) (Scheme 104). However, the efficiency of the catalyst for amide formation was highly ring size depending; thus, while 5-aminopentanol proceeded to full conversion in 4 h, neither 4-amino-1-butanol nor 6-amino-1-hexanol reached 90% conversion after 16 h. Attempts to extend the intramolecular reaction to the corresponding intermolecular case between primary alcohols and amines gave both poor selectivity and yield (Scheme 105). In order to divert the reaction into amide rather than amine, a number of $RHN(CH_2)_5OH$ substrates containing a secondary amine were prepared (Scheme 106). Because of the formation of an imine was no longer possible in such cases, the amine pathway was expected to be forbidden. The complex converted secondary amino alcohols, having *n*-butyl, benzyl, and i-butyl substituents, to the corresponding *N*-substituted valerolactams in high yield in less than 4 h, but branching at the R position reduced the yield, even at longer reaction times.



n	amide	amine	imine
2	70%	20%	-
1	80%	8%	-
0	25%	15%	43%

Reaction conditions: complex (0.025 mmol), substrate (1.0 mmol), KOH (0.07 mmol) in toluene (1 mL) at reflux for 16 h.

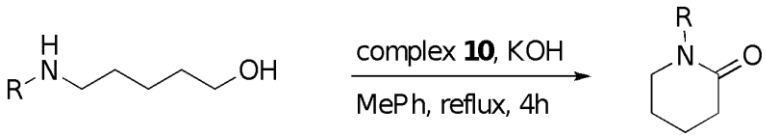
Scheme 104. Ring size dependence in the cyclization of $H_2NCH_2CH_2(CH_2)_nCH_2CH_2OH$ catalyzed by the Ru-complex **10**.



complex[a]	KOH[a]	R	solvent	amide	imine	ester
2.5	8	Ph	toluene	22%	10%	9%
5.0	20	Ph	toluene	42%	2%	9%
2.5	10	*n*-Pr	toluene	10%	48%	-
2.4	11	*n*-Pr	*t*-amyl alcohol	10%	20%	-
2.5	13	*n*-Pr	*p*-xylene	7%	38%	-

Reaction conditions: alcohol (1.0 mmol), amine (1.0 mmol), KOH in 2 mL of the solvent at reflux for 16 h. [a]Loading, mol%.

Scheme 105. Reaction between primary alcohols and amines catalyzed by the Ru-complex **10**.



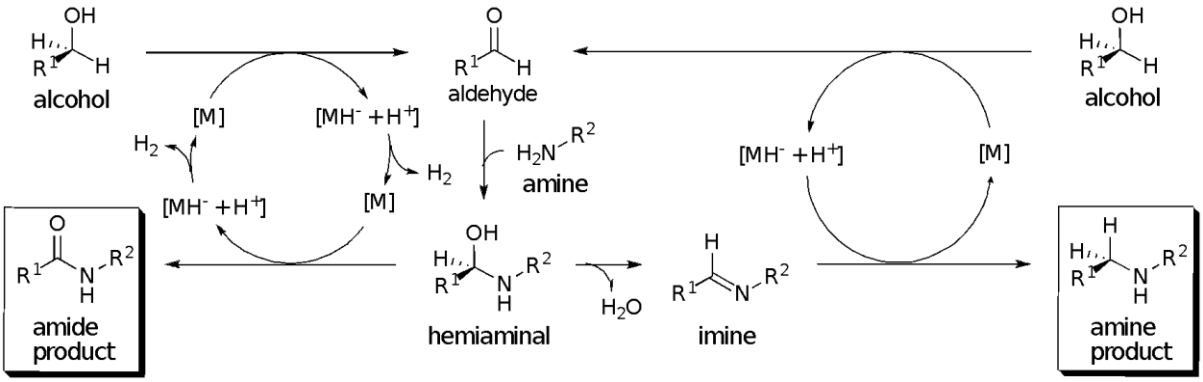
R =*n*-Bu, 84%, R =*i*-Pr, 95%
R =$PhCH_2$, 77%, R = PhCH(Me) 27%[a]
R =*i*-Pr, 21%[a]

Reaction conditions: complex (0.025 mmol), substrate (1.0 mmol), KOH (0.07 mmol) in 1 mL of toluene at reflux for 4 h. [a] Reaction runs for 16 h.

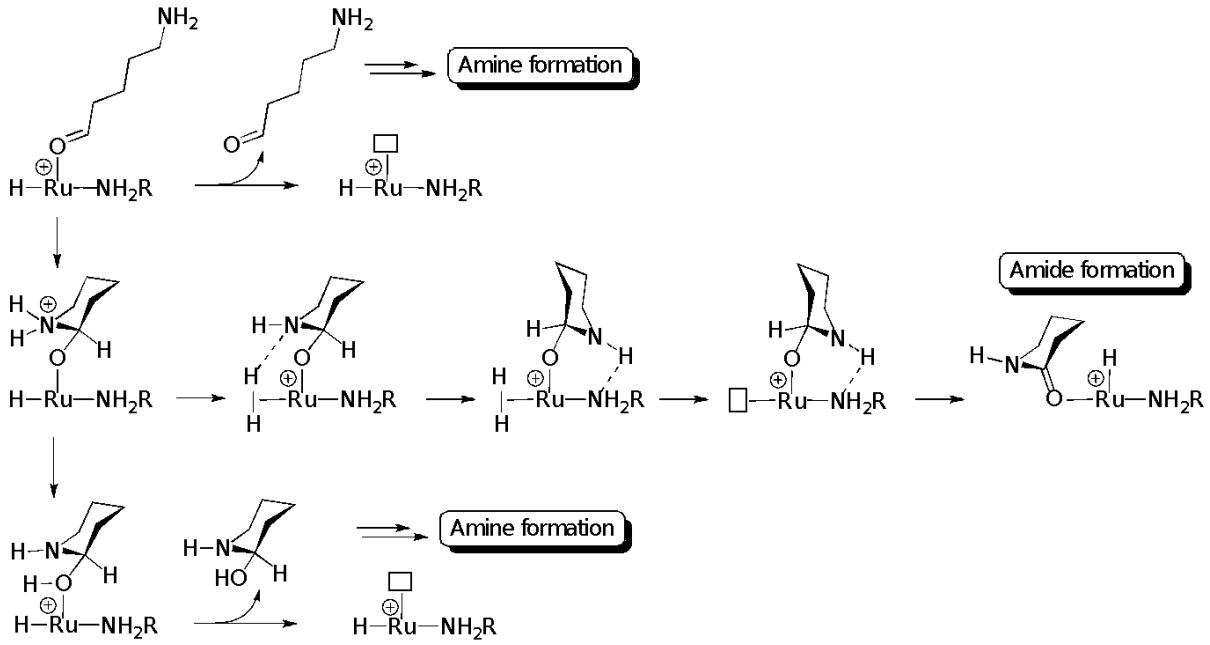
Scheme106. Conversion of amino alcohols to δ-valerolactams catalyzed by the Ru-complex **10**.

A NMR study examining the reaction of 5-amino-1-pentanol under standard reaction conditions revealed signals corresponding to both dissolved H_2 gas and two hydride species. These observations

substantiated the computational results that were carried out. A Ru(II)-diamine complex can catalyze the intramolecular cyclization of amino alcohols $H_2N(CH_2)_nOH$ via two pathways: (i) one yields the corresponding cyclic amide by a net oxidation involving loss of H_2; (ii) the second gives the cyclic secondary amine by a redox-neutral hydrogen-borrowing route with loss of water (Scheme 107, amide (left) and amine (right). The amide and amine pathways are closely related: DFT (density functional theory) calculations showed that both amine and amide formations start with the oxidation of the amino alcohol (e.g. 5-amino-1-pentanol) to the corresponding amino aldehyde, accompanied by reduction of the catalyst (Scheme 108). The intramolecular condensation of the amino aldehyde may take place either in the coordination sphere of the metal (path I) or after dissociation from the metal (path II). Path I yields the Ru-bound zwitterionic form of the hemiaminal protonated at nitrogen, which eliminates H_2, forming the amide product. In path II, the free hemiaminal dehydrates, giving an imine, which yields the amine product by hydrogenation with the reduced form of the catalyst generated in the initial amino alcohol oxidation. For amide to be formed, the hemiaminal must remain metal-bound in the key intermediate and the elimination of H_2 must occur from the same intermediate to provide a vacant site for β-elimination. The elimination of H_2 is affected by an intramolecular H-bond in the key intermediate. For amine to be formed, the hemiaminal must be liberated for dehydration to imine and the H_2 must be retained on the metal for reduction of the imine intermediate. Thus, the amide formation is favoured by catalysts that can retain the aldehyde before the nucleophile addition of the amine but release H_2 from the O-metalated hemiaminal. Cosa vuol dire?



Scheme 107. Pathways proposed for amide (left) and amine (right) formation from alcohols and amines.



Scheme 108. Mechanistic model for the switch between the amide and amine formation reactions.

The same group investigated the contribution of both diamine and diphosphine ligands to the activity of the resulting Ru-complexes for the dehydrogenative oxidation of alcohols to determine the contribution of each ligand to dehydrogenation activity and to identify possible ways to improve the catalysis [77]. Thus, complexes **6**, **10** (Scheme 6), **5**-Me_2 , **17**-Me_2 (Fig. 16) and **18** (Scheme 10), were screened for two related reactions involving alcohol dehydrogenation.

In the intramolecular conversion of *N*-butyl-5-amino-1-pentanol to *N*-butylvalerolactam, complexes **10** and **18** showed to be the most active catalysts, whereas the related derivatives **5**-Me_2 and **17**-Me_2, containing the dimethylated Ampy ligand, gave poor lactam formation (Scheme 109). An intermediate result was obtained by the complex **6**. Complex **18** was also an active catalyst for the amide formation from aliphatic alcohols and amines (Scheme 110), and the dehydrogenative oxidation of 2,5-hexanediol in the presence of a primary alkylamine to give the *N*-alkyl-2,5-dimethylpyrroles (Scheme 111). The chelating Ampy ligand appeared to have a crucial role in certain reactions presented above. The presence of N-H protons make these Ru-complexes superior catalysts, possibly due to a hydrogen-bonding interaction between the ligand and bound substrate which lowers the barrier to hydrogen loss from the metal (Schemes 112 and 113).

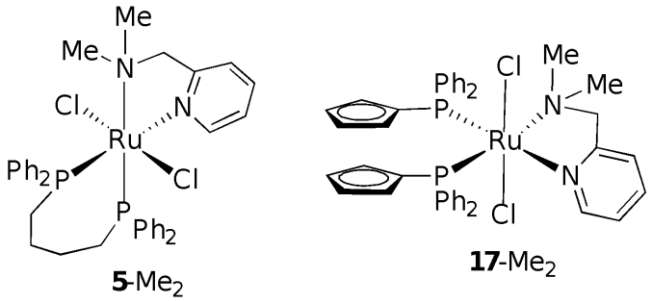
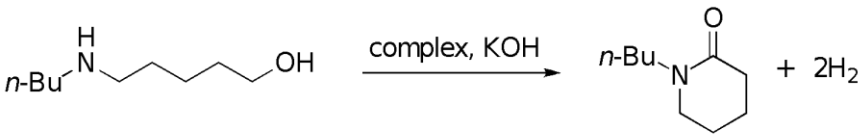


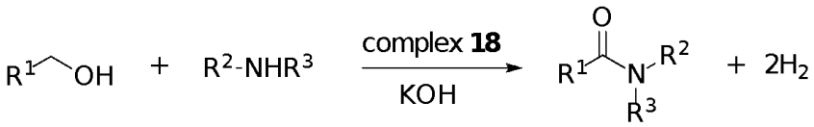
Fig. 16. Chemical structure of the Ru-complexes **5**-Me_2 and **17**-Me_2.



complex	**6**	**10**	**5**-Me_2	**18**	**17**-Me_2
TOF (h^{-1})	40	>120	13	>120	23

Reaction conditions: amino alcohol (1 mmol), KOH (0.06 mmol), complex (0.02 mmol), toluene (1 mL) . The reaction mixture was heated at 125 °C under a slow flow of N_2 for 20 min.

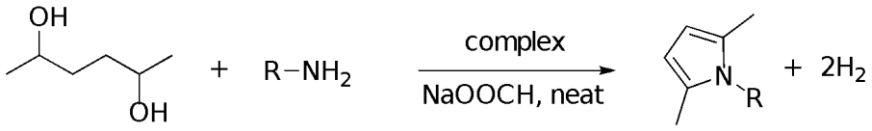
Scheme 109. Comparison of the Ru-complexes **6**,**10**,**5**-Me_2,**18** and **17**-Me_2 for the dehydrogenation of *N*-butyl-5-amino-1-pentanol.



R^1	amine	complex (mol%)	yield (%)
$PhCH_2$	1-hexylamine	2	42
$PhCH_2$	1-hexylamine	4	74
$PhCH_2$	piperidine	2	42
$PhCH_2$	piperidine	4	89
$PhCH_2$	1-decylamine	4	58
$PhCH_2CH_2$	piperidine	4	55

Reaction conditions: alcohol (1 mmol), amine (6 mmol), KOH (0.15 mmol, 4% loading of complex) or KOH (0.1 mmol, 2% loading of complex), complex loading with respect to alcohol substrate, heated at 125 °C for 3.5 h.

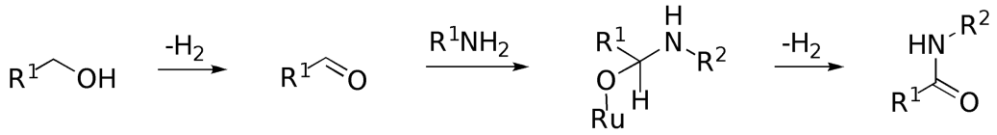
Scheme 110. Intermolecular amide formation catalyzed by the Ru-complex **18**.



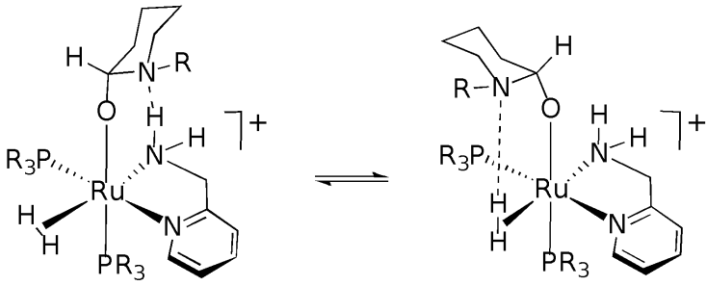
complex	amine	yield (%)
5-Me_2	1-decylamine	37
18	1-hexylamine	45
18	1-decylamine	48

Reaction conditions: 2,5-hexanediol (3.0 mmol), amine (2.5 mmol), sodium formate (0.23 mmol), 1.5 mol% complex loading with respect to amine substrate. The reaction mixture was heated at 125 °C under a slow flow of N_2 for 16 h.

Scheme 111. Dehydrogenative pyrrole formation catalyzed by the Ru-complex **18** and **5**-Me_2.



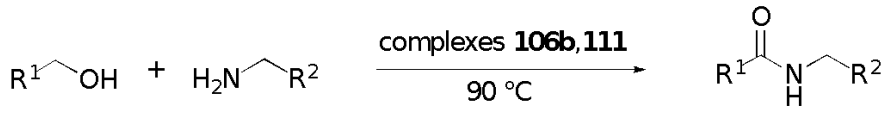
Scheme 112. Amide formation from an alcohol and amine.



Scheme 113. H ydrogen bonding between a bound hemiaminal and either the ligand N-H protons or a dihydrogen ligand.

Very recently Gusev and co-workers reported the application of the Os-complexes **106b** (Fig. 8) and **111** (Scheme 69) in acceptorless dehydrogenative coupling (ADC) of alcohols and amines to amides [48]. Heating ethanol with butylamine or benzylamine with **106b** and NaOEt (1 mol%) (Scheme 114, entries 3-4) selectively produced *N*-butylacetamide and *N*-benzylacetamide, respectively. Methanol gave the corresponding formamides, at a slower rate (entries 1-2), together with *N*,*N*'-dibutylurea and *N*,*N*'-dibenzylurea by-products. *N*-benzylpropionamide and *N*-benzylundec-10-enamide formed selectively (enties 7–8). However, propanol and 10-undecenol with butylamine gave mixtures of the corresponding amide and imine products, in low yields (entries 5–6, 9–10). The experimental evidences were indicative of competing catalytic pathways, where the more efficient path leads to amides, whereas the imine formation might be inhibiting the catalyst.

It should be noted that the complex **106b** efficiently operates at relatively low temperatures (e.g. with ethanol, b.p. = 78 °C) without solvent and without argon flow. Entries 5–6 of Scheme 114 are the first preparative examples of ADC of MeOH with amines, affording formamides. Data obtained by carrying out NMR, ESI-MS and DFT experiments indicated a catalytic mechanism proceeding entirely in the metal coordination sphere and producing no free organic intermediates.



entry	R^1	R^2	R^1/R^2 [a]	complex[b]	time (h)	base[c]	conv[d]
1	H	Pr	90/80	**106b**, 1.0	19	NaOMe, 2	78[e]
2	H	Ph	90/80	**106b**, 1.0	19	NaOMe, 2	68[f]
3	Me	Pr	80/80	**106b**, 0.05	17	NaOEt, 1	90
4	Me	Bn	80/80	**106b**, 0.05	17	NaOEt, 1	96
5	Et	Pr	60/60	**106b**, 0.05	17	KO*t*-Bu, 1	43[g]
6	Et	Pr	60/60	**111**, 0.05	16	none	39[g]
7	Et	Ph	60/60	**106b**, 0.05	17	KO*t*-Bu, 1	90
8	$C_{10}H_{19}$	Ph	40/40	**111**, 0.05	18	none	88[h]
9	$C_{10}H_{19}$	Pr	40/40	**106b**, 0.05	16	NaOMe, 1	15[i]
10	$C_{10}H_{19}$	Pr	40/40	**111**, 0.05	22	none	19[i]

[a]Substrates (mmol); $C_{10}H_{19}$ = dec-9-enyl. [b]Complex, mol%. [c]Base, mol%. [d]Conversion to amide. [e]Plus 18% of *N,N*-dibutylurea; distilled *N*-butylformamide 75%. [f]Plus 12% of *N,N*-dibenzylurea, distilled *N*-benzylformamide yield: 51%. [g]Plus 6% of the imine. [h]P = 11 torr, isolated amide yield: 83%, 3.5% C-10 to C-9 olefin isomerization. [i]Plus about 5% of the imine.

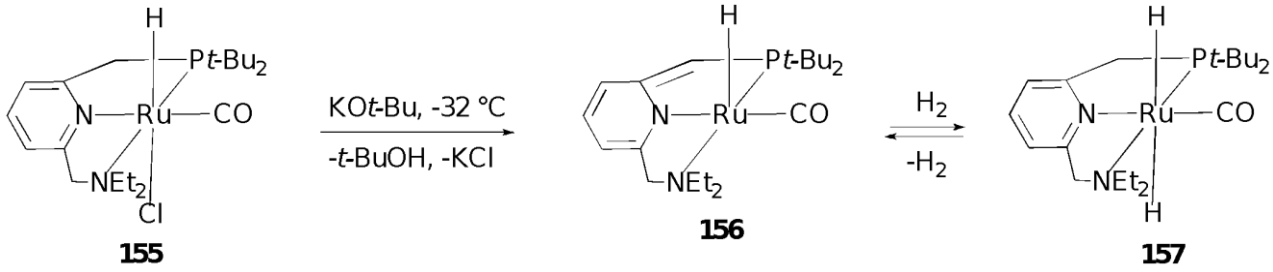
Scheme 114. Dehydrogenative coupling of alcohols and amines to amides catalyzed by the complexes **106b** and **111**.

14. Synthesis of esters from alcohols

Milstein and co-workers reported Ru-complexes that efficiently and selectively catalyzed the dehydrogenation of primary alcohols to esters and H_2 under relatively mild, neutral conditions [78]. The complex **155** was obtained in 90% yield when the PNN ligand (2-(di-*tert*-butylphosphinomethyl)-6-diethylaminomethyl)pyridine was treated with $RuHCl(CO)(PPh_3)_3$ (Scheme 115). Complex **155** in the presence of 1 equiv of base showed to be an efficient dehydrogenative esterification catalyst. Thus, upon heating a 0.1 mol% solution of **155** with KOH (1 equiv relative to Ru) in 1-hexanol at 157 °C under argon for 24 h, hexyl hexanoate was formed in 91.5% with a trace of 1-hexanal (Scheme 116). The temperature could be lowered to 115 °C in refluxing toluene, resulting in 94.5% yield (TOF = 945) to the ester after the same period. Other alcohols reacted similarly (Scheme 116). Since no reaction took place in the absence of base, attempts were aimed at totally eliminating the need for a base. Exploring the possibility that the reaction of **155** with the base could afford the corresponding Ru(0)-

complex, **155** was treated with 1 equiv of KO *t*-Bu at -32 °C. Interestingly, deprotonation of the benzylic phosphine "arm", rather then the hydride ligand, took place, resulting in the brown-red Ru(II) complex **156** in 89% yield (Scheme 115). Moreover, reaction of complex **156** with H_2 resulted in aromatization, yielding the *trans*-dihydride complex **157** that slowly loses H_2 at room temperature to regenerate complex **156** (Scheme 114). Complex **156** was the best homogeneous catalyst for acceptorless dehydrogenative esterification of alcohols. When it was used as catalyst without any base, ester yields of over 90% (TON > 900) were obtained from the alcohols in relatively short reaction times (Scheme 116). Some experiments appeared to indicate that the reaction proceeds by dehydrogenation to the aldehyde followed by hemiacetal formation from the aldehyde and alcohol followed by its dehydrogenation to the ester.

Complex **156** was next used in a number of chemical transformations [79].



Scheme 115. Synthesis of the Ru-complexes **155** and **156**.

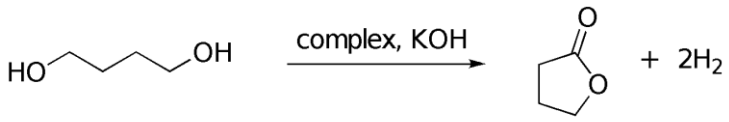
$RCH_2OH \xrightarrow[KOH,\ 115\text{-}157\ °C]{\text{complexes } \mathbf{155},\mathbf{156}} RCO_2CH_2R + H_2$

complex	R	KOH (equiv)	temp (°C)	time (h)	conv (%)	yield (%) (ester)	yield (%) (aldehyde)
155	*n*-C_5H_{11}	1	157	24	90.4	90	0.3
155	*n*-C_5H_{11}	0	157	24	0	0	0
155	*n*-C_5H_{11}	1	115[a]	24	95	94.5	0.1
155	*n*-C_5H_{11}	1	117	72	92.5	91.5	1
155	Ph	1	115[a]	72	100	99.5	0
156	*n*-C_5H_{11}	0	117	5	91	90	0.5
156	*n*-C_5H_{11}	0	157	2.5	91.5	91.4	0.1
156	*n*-C_5H_{11}	0	115[a]	6	99	99	0
156	Ph	0	115[a]	4	93.3	92.1	1

Reaction conditions: complex (0.01 mmol), KOH (0.01 mmol) and alcohol (10 mmol) were heated neat under Ar flow. [a]Toluene (2 mL) was added, and the solution was refluxed.

Scheme 116. Dehydrogenation of primary alcohols to esters and H_2 catalyzed by the complexes **155** and **156**.

Crabtree and co-workers investigated the contribution of both the diamine and diphosphine ligands to the activity of $RuCl_2(PP)(NN)$ complexes for the dehydrogenative oxidation of alcohols [76]. Complexes **6**,**10**,**5**-Me_2,**18**, and **17**-Me_2 were screened for the dehydrogenation of 1,4-butanediol to γ-butyrolactone (Scheme 117). Complexes **10** and **18** showed to be the most active catalysts, whereas the use of the related dimethylated Ampy ligands (**5**-Me_2 and **17**-Me_2) dramatically decreased the rate of lactone formation. The complex **6** afforded an intermediate result.

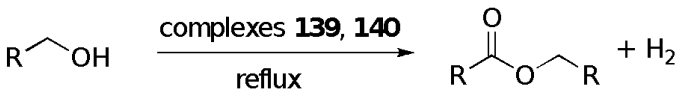


complex	**6**	**10**	**5**-Me_2	**18**	**17**-Me_2
TOF (h^{-1})	5.0	10	5.9	12	1.5

Reaction conditions: diol (2 mmol), KOH (0.10 mmol), complex (0.02 mmol) in toluene (1mL). The reaction mixture was heated at 125 °C under a slow flow of N_2 for 4 h.

Scheme 117. Comparison of the Ru-complexes **10**,**5**-Me_2,**18**,**17**-Me_2 and **6** for the dehydrogenation of 1,4-butanediol.

Gusev and co-workers tested the activity of the Os- and Ru-complexes **139** and **140** (Fig. 11), respectively, as catalysts for ADC of alcohols (Scheme 118) [56]. It was found that the catalytic activity of **139** was particularly impressive in ethanol and propanol at 78 and 96 °C as conversions of these alcohols to ethyl acetate and propyl propionate.

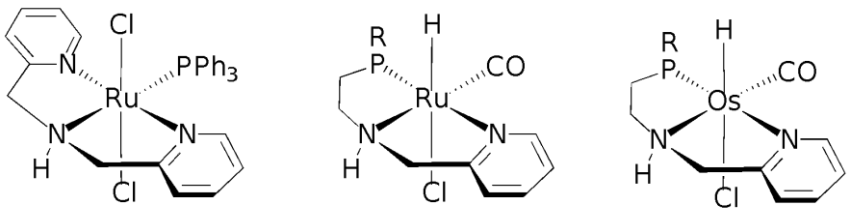


R	complex	temp (°C)	time (h)	conv (%)
Me	**139**	78	24	7
Me	**139**[a]	78	8	61
Me	**139**[a,b]	78	8	96
Me	**140**[b]	78	7.5	30
Et	**139**	96	8.5	86
Et	**140**[b]	96	8	73
Pr	**139**	118	3	93
Pr	**140**[b]	118	3	78
i-amyl	**139**	131	3	86
i-amyl	**140**[b]	131	2.5	92
hexyl	**139**	158	1.3	97
hexyl	**139**[c]	158	1.3	71
hexyl	**140**[b]	158	1	86

Reaction conditions: neat substrate (52 mmol), molar ratio substrate/metal = 1000, reflux. [a]In toluene (3 mL). [b]With KO*t*-Bu (0.5 mol%). [c]Molar ratio substrate/metal = 4000.

Scheme 118. Acceptorless dehydrogenation of alcohols to esters catalyzed by the Ru- and Os-complexes **139** and **140**.

Next, Ru- and Os-complexes **142**,**157-162** (Fig. 17) were assessed in ethanol dehydrogenation [58]. The results, summarized in Scheme 119, were obtained by carrying out the reactions at reflux temperature using 0.05 mol% of the complex in the presence of 1 mol% of NaOEt. These experiments unambiguously established the superior efficiency of the Ru-complex **142** that consistently afforded high yields of ethyl acetate. This catalyst with 0.005 mol% loading also produced 17.000 turnovers in 40 h and gave 83% of ethyl acetate, suggesting that **142** is both a remarkably efficient and a highly robust catalyst.

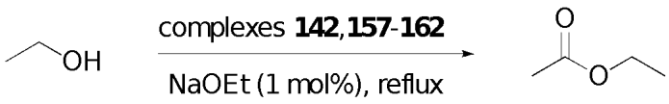


157

158: R = Ph_2
159: R = *t*-Bu_2

160: R = Ph_2
161: R = *i*-Pr_2
162: R = *t*-Bu_2

Fig. 17. Chemical structure of the Ru- and Os-complexes **157-162**.

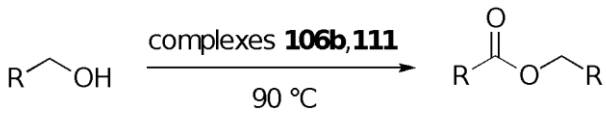


complex (mol%)	EtOH (mol)	time (h)	conv (%)
142 (0.05)	0.1	16	95
142 (0.01)	0.2	24	91
142 (0.005)	0.2	40	85
157 (0.05)	0.1	16	0
158 (0.05)	0.1	16	41
159 (0.05)	0.1	16	12
160 (0.05)	0.1	16	40
161 (0.05)	0.1	16	27
162 (0.05	0.1	16	20

Reaction conditions: reflux (presumably 71.8 °C, the boiling point of ethanol/ethyl acetate mixtures).

Scheme 119. Acceptorless dehydrogenation of ethanol to give ethyl acetate catalyzed by the Ru- and Os-complexes **142**,**157**-**162**.

The same group very recently reported the application of the Os-complexes **106b** (Fig. 8) and **111** (Scheme 69) in the ADC of alcohols [48]. Indeed, by heating ethanol with **106b** and NaOEt (1 mol%) at 90 °C, the ADC was complicated by formation of ethylbutyrate (1.9%) and traces of unidentified organic compounds, in addition to ethylacetate (82% conv) (Scheme 120). Whereas, ethylacetate was obtained with 9.000 turnovers by refluxing **111** in ethanol. This complex also efficiently catalyzed t he ADC of propanol and 10-undecenol (Scheme 69) .



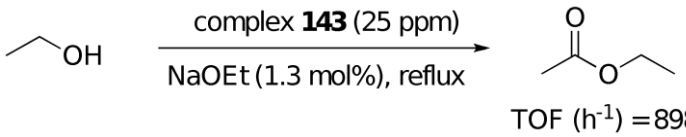
entry	R	complex[a]	time (h)	base[b]	conv (%)[c]
1	Me	**106b**, 0.01	24	NaOEt, 1	82
2	Me	**111**, 0.01	24	none	90
3	Et	**111**, 0.01	21	none	69[e]
4	$C_{10}H_{19}$[d]	**111**, 0.02	18	none	94[f]

[a]Complex, mol%. [b]Base, mol%. [c]Conversion to ester. [e]At 100 °C. [f]P = 2 torr, 1.5% C-10 to C-9 olefin isomerization. [d]$C_{10}H_{19}$ = dec-9-enyl.

Scheme 120. Dehydrogenative coupling of alcohols to esters catalyzed by the complexes **106b** and **111**.

Beller and co-workers also investigated the catalytic ADC of ethanol to ethyl acetate (Scheme 121) [80]. Among the six examined ruthenium and iridium catalysts the pincer complex **143** (Fig.

14) showed good activity, although a lower level than that of the other assessed complexes.



Scheme 121. Dehydrogenative coupling of ethanol to give ethyl acetate catalyzed by the complex **143**.

15. Conclusions

The discovery that 2-(aminomethyl)pyridine (Ampy) based ruthenium and osmium complexes have showed a remarkably high catalytic activity in hydrogenation by dihydrogen (HY) and transfer hydrogenation (TH) of carbonyl compounds has allowed the designing of a new family of fast and highly productive catalysts for the synthesis of chiral and non-chiral alcohols. Moreover, the use of these complexes has been profitably extended to other metal-catalyzed organic transformations involving alcohols and carbonyls such as dehydrogenation, racemisation and alkylation, etc.

From the number of catalytic reactions reported in this account and the excellent results that have been obtained by these ruthenium and osmium Ampy based complexes, it results that they play a important role in asymmetric and non-asymmetric catalysis. The use of these complexes and their further development is certainly of great interest in the search of novel opportunities for new catalytic processes as well as for improvement of the existing ones.

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