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1-(Pyridin-2-yl)methanamine-Based Ruthenium Catalysts for Fast Transfer Hydrogenation of Carbonyl Compounds in 2-Propanol

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This Microreview focuses on the development of novel ruthenium complexes displaying high performance in the catalytic asymmetric transfer hydrogenation of ketones with 2-propanol, providing this procedure alternative to the hydrogenation with dihydrogen. The key role is played by 1-(pyridin-2-yl)methanamine (Pyme) type ligands which in combination with appropriate phosphanes afforded ruthenium systems of unprecedented high catalytic activity and productivity for the reduction of ketones and aldehydes. For the pincer CNN complexes a mixed inner-outer sphere mechanism involving Ru-hydride and Ru-alkoxide species is proposed. The excellent properties of these complexes are expected to have implications for the design of a new generation of catalysts.

1. Introduction

Asymmetric hydrogenation (HY)[1] and transfer hydrogenation (TH)[2] of carbonyl compounds catalyzed by transition metal complexes are among the most important transformations to prepare alcohols in high enantiopure form. These reactions have widely been investigated in the past and a large number of simple and functionalized carbonyl compounds have been reduced through the development of novel efficient catalysts and the optimization of the catalytic reaction conditions. Among the different metals used in HY and TH, particular attention has been payed to rhodium, iridium, and ruthenium complexes. In the 1990s, a crucial improvement in the development of highly active metal systems for the asymmetric reduction of simple carbonyl compounds has been given by Noyori and co-workers who observed that NH_2 amine ligands accelerate the catalytic HY and TH of ketones.[1c,2i] Evidence has been provided that during catalysis the *cis*-Ru–H/–NH_2 motif plays a fundamental role through a concerted delivery of a N–H proton and a Ru–H hydride, via an outer sphere mechanism (metal-ligand bifunctional catalysis).[3] Notably, in the 1980s Shvo and co-workers developed a cyclopentadienyl ruthenium catalyst for the reduction of ketones in which the TH occur in a concerted pathway.[4]

The catalytic asymmetric HY of carbonyl compounds entails the use of dihydrogen under pressure and represents the most attracting industrial process for synthesis of chiral alcohols due to the fact that hydrogen is the cleanest reducing agent (Scheme 1).

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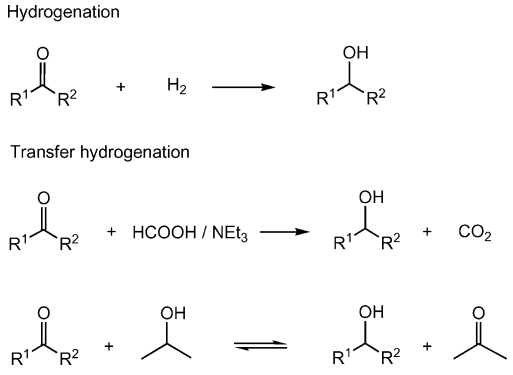
Walter Baratta was born in Bolzano (Italy) in 1964. In 1983 he obtained a fellowship from the Scuola Normale Superiore of Pisa and in 1989 graduated from the University of Pisa. He completed his Ph. D. in Chemistry under the supervision of Prof. F. Calderazzo (Pisa) and spent one year in the group of Prof. P. S. Pregosin at the Technical Institute of Zürich. He carried out postdoctoral studies in the laboratory of Prof. W. A. Herrmann at the Technical Institute of Munich (Alexander von Humboldt fellowship). After returning to Italy he became Research Associate in 1996 in the group of Prof. P. Rigo at the University of Udine and in 2005 was appointed Associate Professor. His research interests are mainly focused on homogeneous catalysis, with particular regard to the development of new efficient catalytic systems for transfer hydrogenation and hydrogenation reactions.

Pierluigi Rigo was born in Montereale Valcellina (Pordenone - Italy) in 1940. He obtained the degree in Chemistry in 1964 at the University of Padova, where he became assistant professor, then lecturer and Libero Docente (1969) of General and Inorganic Chemistry. In this period he worked at the Centro di Studio sulla Stabilità e Reattività dei Composti di Coordinazione of the CNR of Padova and he was Member of the Scientific Council. Since 1980 he is full professor of General and Inorganic Chemistry at the University of Udine. His research interest has been primarily focused on the chemistry of group VIII metal complexes with phosphorus ligands and their applications as catalysts in organic synthesis. The current research program includes in particular the study of the catalytic potential in hydrogenation and hydrogen transfer reactions of transition metal systems with phosphanes and diamines. Author of about 120 publications in Inorganic and Organometallic Chemistry.



Scheme 1. Hydrogenation and transfer hydrogenation of carbonyl compounds.

A particularly successful outcome was the preparation of the highly enantioselective and productive hydrogenation catalysts *trans*-[$RuCl_2$(diphosphane)(diamine)],[1c,5] showing an appropriate combination of bidentate chiral ligands. This fundamental work has led to the designing of different efficient catalytic systems for specific substrates.[1]

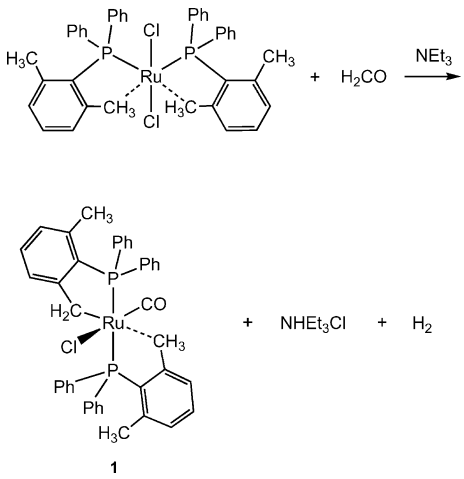
The catalytic TH of ketones is usually carried out by using formic acid or 2-propanol as hydrogen sources in basic media (Scheme 1). With HCO_2H the ketones are straightforwardly converted into alcohols with formation of carbon dioxide/hydrogen carbonate, according to the basicity of the media.[6] Employment of 2-propanol which is not toxic and easy to handle requires an excess of alcohol to shift the equilibrium to the desired product. For acetophenone with an initial concentration of 0.1 M the equilibrium mixture 1-phenylethanol/acetophenone is 98:2, while this ratio is 80:20 when the ketone is 1 M (Scheme 1).[2i] Therefore, the reduction of ketones is usually carried out with a substrate concentration of about 0.1 M or at higher concentrations by removing acetone from the reaction mixture by exploiting its lower boiling point compared to 2-propanol (56 vs. 82 °C). Primary alcohols (i.e. ethanol or methanol) are generally not employed as hydrogen donors because of the unfavorable redox potential of the primary vs. secondary alcohols.[7] Furthermore, the resulting aldehydes are susceptible in basic media to deprotonation of the hydrogens of the α-CH group, leading to aldol condensation and may also undergo decarbonylation reactions with deactivation of the catalysts.[8] Recently, ethanol has been used efficiently as reducing agent in catalytic TH with concomitant formation of ethyl acetate.[9] In the past years the intense research efforts in TH have resulted in the development of new catalysts displaying high turnover number (TON) and turnover frequency (TOF), in addition to high enantioselectivity. The well-known system [RuCl(LL)(η^6-arene)] (LL = β-amino alcohol, diamine),[10] reported by Noyori and co-workers, has inspired the development of numerous ruthenium-arene complexes based on chiral bidentate ligands. Particularly attracting are the systems with NN and NO ligands,[11] BINOL-diphosphonite,[12] tethered ligands,[13] and those containing ruthenacycles.[14] In addition, interesting results have been obtained with the catalysts of general formula [$RuCl_2(PR_3)$(L)] (L = PN[15] and NNN[16] oxazoline ligands) and the tetradentate complexes [$RuCl_2$(PNNP)].[17] Although these systems exhibit high enantioselectivity for the reduction of ketones, both speed (TOF $< 10^4$ h^{-1}) and productivity (TON $\leq 10^4$) remain low. By contrast, a higher activity has been reported for the achiral systems [$RuCl_2(PR_3)$(L)] (L = PN and PNO,[18] NPN[19]), [RuCl(PCP)(P)][20] and the zwitterionic complex [RuCl(PN)(η^6-arene)][21] (TOFs up to 2.7×10^5 h^{-1}). According to the discovery by Chowdhury and Bäckvall in the early 1990s that the catalytic activity of [$RuCl_2(PPh_3)_3$] is significantly increased by addition of NaOH, all these catalytic systems require the use of a strong base (alkali metal hydroxide or alkoxide) to generate the catalytically active ruthenium hydride species.[22] At this regard, NaOH in 2-propanol has been proven to slowly catalyzes the TH of ketones,[23] in agreement with the Meerwein–Ponndorf–Verley reaction mediated by aluminum and other main group element alkoxides.[24]

On account of its operational simplicity, mild methodology and absence of the risks associated with the use of dihydrogen, the asymmetric TH is being increasingly used in industrial plants for the preparation of chiral alcohols which are building blocks of valuable products, such as NK-1 receptor antagonists, agrochemicals and chiral amines.[25] Therefore, the TH is becoming an important process for the synthesis of fine chemicals and can be competitive with respect to HY. Furthermore, the different stereo-, chemo-, and regioselectivity of the TH compared to HY, indicate that the two processes may be complementary.

In this account, we summarize our efforts toward the designing of a new class of highly active ruthenium catalysts for the TH of carbonyl compounds based on the 1-(pyridin-2-yl)methanamine (Pyme) motif.[26] These complexes display remarkably high activity, productivity (TOF[27] and TON up 10^6 h^{-1} and 10^5, respectively) and enantioselectivity when an appropriate combination of chiral ligands is chosen. Kinetic studies indicate that ruthenium-alkoxides and hydrides are key species involved in the catalytic cycle and a mixed inner/outer sphere mechanism has been proposed.

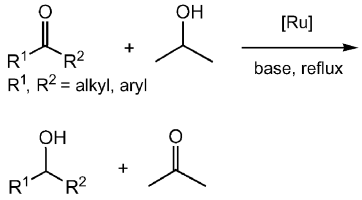
2. Pyme as Accelerating Ligand for TH

Our research on the TH of ketones began with the study of the reactivity of a rare example of a 14-electron ruthenium complex [$RuCl_2${(2,6-$Me_2C_6H_3$)PPh_2}$_2$], stabilized by two non-classical (M···η^3-H_2C) δ-agostic interactions of *ortho* methyl groups.[28] Interestingly, this compound easily reacts with formaldehyde in the presence of a weak base affording the 16-electron monocarbonyl complex **1** in which one phosphane is cyclometalated while the other one shows one methyl group that interacts with the metal in an agostic fashion [Equation (1)].[29]



(1)

It is worth noting that pincer PCP ruthenium derivatives,[30] displaying a metal–carbon σ-bond, have extensively been investigated for both stoichiometric and catalytic reactions. On the other hand, simple cyclometalated ruthenium systems have sparingly been used in catalysis (e.g. olefin hydrogenation)[31] and therefore the development of simple routes to achieve PC complexes,[32] showing features similar to PCP, would prove to be useful. In order to investigate the potential of complex **1** in homogeneous catalysis, we observed that in the presence of a strong base (NaOH, 2 mol-%) this compound showed a moderate activity in the TH of ketones with 2-propanol at reflux. By using 0.2 mol-% of **1**, acetophenone is reduced with a TOF of 3×10^2 h^{-1} [Equation (2)].

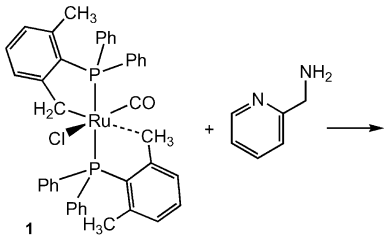


(2)

Compound **1**, which shows a cyclometalated phosphane and CO ligand with a *fac* relationship, appeared to be a good precursor for the catalytic TH studies because of the presence of one chloride that can be converted into hydride during catalysis and a weakly coordinated bulky phosphane which allows a flexible substitution pattern. Thus, the bulky phosphane occupying two coordination sites can easily be displaced by two mono or a bidentate phosphorus and nitrogen containing ligands, affording a large number of cyclometalated complexes of formula [RuCl{(2-CH_2-6-MeC_6H_3)PPh_2}(CO)L_2] (L = monodentate or L_2 = bidentate ligand). These species were quickly generated in situ and tested in TH, without isolation of the complexes, reducing the time necessary for the search of the most favorable combination of ligands. With the phosphanes $PMePh_2$ and $Ph_2P(CH_2)_4PPh_2$ we did not observed a significant improvement of the rate for the TH of acetophenone, respect to **1**. Also monodentate nitrogen ligands, such as Et_2NH, $Me_2CHCH_2NH_2$, $PhCH_2NH_2$ led only to a slightly increase of the speed of the reaction, whereas the TOF doubled with the bidentate amines $HMeN(CH_2)_2NMeH$ and $Me_2N(CH_2)_2NH_2$. A significant rate enhancement was observed with $H_2N(CH_2)_2NH_2$, which gave a TOF = 2800 h^{-1}, in agreement with the well-known studies of Noyori and co-workers on the Ru-NH_2 systems.[2i] With pyridine the TOF was 900 h^{-1}, whereas bipyridine and phenanthroline led to a small increase of the catalytic activity of **1**. A remarkable result was obtained through the combination of **1** with the mixed pyridine-amine ligand Pyme that afforded one of the most active system reported at that time, with the complete conversion of acetophenone in 5 min (TOF = 6.0×10^4 h^{-1}) with 0.05 mol-% of Ru. These data can be compared with those reported by the groups of Mathieu, Braunstein and van Koten for the reduction of MeCOPh with [$RuCl_2(PR_3)(L)$] (L = PNO,[18b] NPN[19]), [$Ru(O_3SCF_3)$(PCP)(P)],[20] leading to TOF/10^4 = 9.0, 7.0 and 0.9 h^{-1}, respectively. At 0.01 mol-% loading of **1**/Pyme, complete conversion of acetophenone (98%) was achieved in less than 1 h, suggesting that the catalytically active species is relatively robust (i.e. deactivation occurs slowly), on account of the presence of the cyclometalated phosphane. Without base, the system **1**/Pyme is practically not active, suggesting that during catalysis in the basic alcohol media the ruthenium chloride is converted into hydride and alkoxide species (see further part). It is worth noting that the use of the related ligand 2-(pyridin-2-yl)ethanamine resulted in a much less active system (TOF of about 4×10^3 h^{-1}), indicating that the length of the chain is crucial for the activity. Previous studies on the asymmetric TH using in-situ-generated ruthenium species with related Pyme ligands have been reported by Mizushima et al., Moreau et al. and Brunner et al., but the full potential of the commercially available simple Pyme was not recognized.[33] Therefore, this study led to the discovery of an accelerating ligand suitable for the cyclometalated-ruthenium framework, thus associating high speed and productivity which are prerequisites for highly efficient catalytic systems. Subsequently, the complex **2** was isolated from **1** and Pyme and its structure was definitively established in solution through a ROESY experiment [Equation (3)].

Compound **2** displays the same activity of **1**/Pyme and was proven to catalyze the quantitative TH of a large number of aliphatic (linear and cyclic) and aromatic ketones in a few minutes, affording TOFs up to 6.3×10^4 h^{-1}. Some examples are given in Table 1.

Chemoselective C=O reduction was also observed for olefinic ketones such as 5-hexen-2-one for which no C=C reduction or isomerization occurs. Diaryl ketones which are substrates difficult to reduce have selectively been converted to benzhydrols and this reaction was proven to be efficient even at low loading of catalyst (0.01 mol-%, 2 h), indicating that TH is a valid alternative to HY for the synthesis of relevant intermediates. Interestingly, also bulky ketones, such 3,3-dimethyl-2-butanone, 2,2-dimethylpropiophenone and menthone, which are feebly reactive in the TH,[34] were



(3)

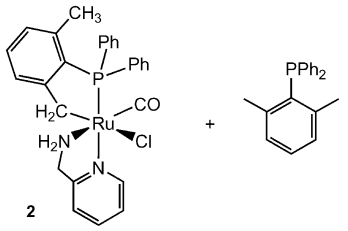
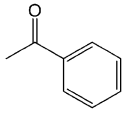
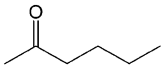
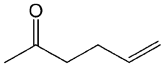
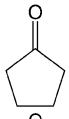
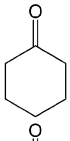
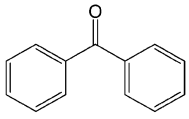


Table 1. Catalytic TH of ketones with **2** at 0.05 mol-%.[a]

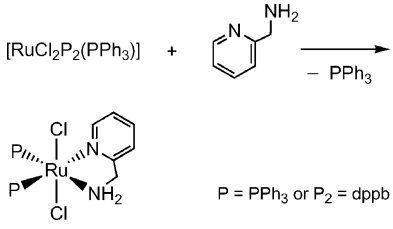
Ketone	Conversion [%]	[min]	TOF [h^{-1}]
	98	5	6.0×10^4
	99	10	6.3×10^4
	95	10	3.0×10^4
	99	10	3.4×10^4
	99	15	1.9×10^4
	95	5	3.6×10^4

[a] Ketone 0.1 M and NaOH 2 mol-% in 2-propanol at T = 82 °C.

reduced quantitatively to alcohols with **2** (TOF/10^4 = 0.9–2.0 h^{-1}). The lower rate observed in the latter case is ascribed to the high steric crowding of the ketone that impedes the access of the carbonyl group to the metal center. The robustness of the system **2** is due to the strong Ru–carbon bond which is 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 Pyme 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.

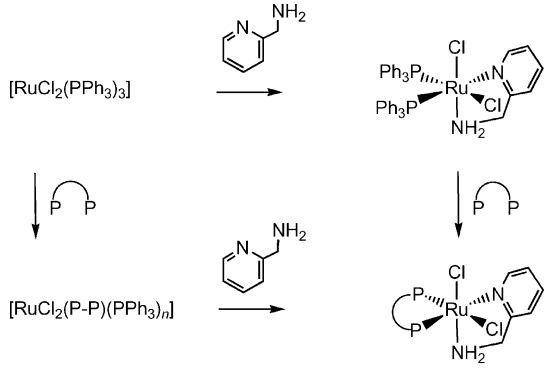
3. Ruthenium Complexes [RuX_2P_2(Pyme)] (X = Cl, H)

The excellent catalytic performance of the Pyme-based cyclometalated ruthenium compound **2** prompted us to develop new Pyme ruthenium catalysts. One of the most well-known ruthenium precursor is [$RuCl_2(PPh_3)_3$] which can easily reacts with phosphorus and nitrogen ligands by displacement of PPh_3.[35] Since, preliminary catalytic results showed that the in-situ-prepared [$RuCl_2(PPh_3)_3$]/Pyme system is catalytically active in the TH of acetophenone, we decided to prepare a series of complexes of general formula [$RuCl_2P_2$(Pyme)][36] (P = phosphane or P_2 = diphosphane). At room temperature the precursors [$RuCl_2(PPh_3)_3$] and [$RuCl_2(PPh_3)$(dppb)] {dppb = $Ph_2P(CH_2)_4PPh_2$} react with Pyme, affording the derivatives *trans*-[$RuCl_2P_2$(Pyme)] [Equation (4)].



(4)

The thermodynamically most stable complexes *cis*-[$RuCl_2P_2$(Pyme)] were obtained by treatment of [$RuCl_2(PPh_3)_3$] with Pyme in toluene at reflux and by addition of a suitable achiral or chiral diphosphane, namely $Ph_2P(CH_2)_n$-PPh_2 (n = 3, 4), (*S*,*S*)-Skewphos, (*R*,*R*)-Diop (Scheme 2).



Scheme 2. Preparation of *cis*-[$RuCl_2P_2$(Pyme)].

With bulky phosphanes, such as (*R*,*S*)-Josiphos, these Pyme compounds can be obtained by reversing the order

of the reactants. It is worth noting that with the optically active diphosphanes a single stereoisomer is formed in solution, as inferred from NMR spectroscopy. Compounds $[RuCl_2P_2(Pyme)]$ display good to very high catalytic activity in the TH of ketones in 2-propanol at reflux and in the presence of NaOH. The *cis* complexes were proven to be more active than the corresponding *trans* isomers and the best performances were obtained with diphosphane ligands. For example *cis*-$[RuCl_2(dppb)(Pyme)]$ (**3**) at 0.05 mol-% catalyzes the quantitative TH of acetophenone in 1 min, affording a TOF value of 3.0×10^5 h^{-1} (Figure 1).[36]

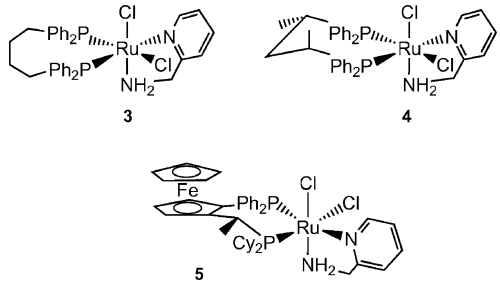


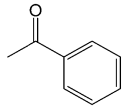
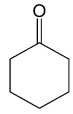
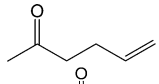
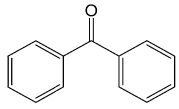
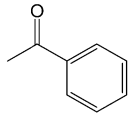
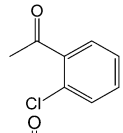
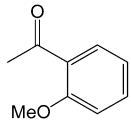
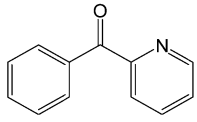
Figure 1. *cis*-$[RuCl_2(PP)(Pyme)]$ complexes.

With **3** numerous ketones, such as cyclohexanone, 5-hexen-2-one, and benzophenone were quantitatively and chemoselectively reduced to give the corresponding alcohols within 10 min and with TOF values up to 4.0×10^5 h^{-1}, the latter being the highest value reported at that time (Table 2).[37a]

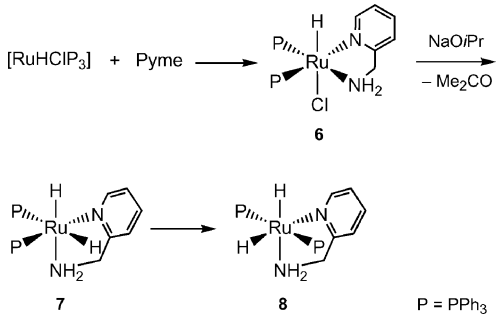
The comparison of the activity of the related diamine complex *trans*-$[RuCl_2(dppb)\{H_2N(CH_2)_2NH_2\}]$ affords a TOF of about 10^3 h^{-1} under the same experimental conditions. This data agrees with those of Lindner et al. and Morris et al. on the complexes *trans*-$[RuCl_2P_2(1,2\text{-diamine})]$ which are highly active HY catalysts but display moderate activity in TH.[17c,37b] This indicates that Pyme shows a strong ligand acceleration effect in the TH reaction, as observed for the cyclometalated complex **1**. Fast and asymmetric TH of methyl aryl ketones was observed using the chiral derivative *cis*-$[RuCl_2\{(S,S)\text{-Skewphos}\}(Pyme)]$ (**4**). Thus, acetophenone is reduced with **4** (0.05 mol-% at 82 °C) to (*S*)-1-phenylethanol in 1 min (TOF = 3.0×10^5 h^{-1}) with 85% *ee* and no erosion of enantioselectivity occurs at lower catalyst loading (0.01 mol-%). The o*rtho* substituted ketones 2′-chloroacetophenone and 2′-methoxyacetophenone were quickly reduced to the corresponding (*S*)-alcohols with *ee* up to 94%, whereas (*S*)-phenyl(2-pyridyl)-methanol (90% *ee*) was obtained from the corresponding pyridyl ketone.[38] Employment of *cis*-$[RuCl_2\{(R,S)\text{-Josiphos}\}(Pyme)]$ (**5**) resulted in the TH of acetophenone to (*S*)-1-phenylethanol in 2 min with 83% *ee*.

Since $[RuCl_2P_2(Pyme)]$ are not active in TH without base, we decided to prepare the mono and dihydride complexes of the type $[RuH_nCl_{2-n}(PPh_3)_2(Pyme)]$ (n = 1, 2), following the studies of Bäckvall on $[RuCl_2(PPh_3)_3]$. As a matter of fact, the dihydride derivative $[RuH_2(PPh_3)_4]$, which is formed from $[RuCl_2(PPh_3)_3]$ in basic alcohol media through a β-hydrogen elimination reaction,[39] was found to be the catalytically active species.[40] The monohydride *trans*,*cis*-$[RuHCl(PPh_3)_2(Pyme)]$ (**6**), prepared from $[RuHCl(PPh_3)_3]$ and Pyme, catalyzed the TH of ketones only by addition of base (Scheme 3).[36]

Table 2. Catalytic TH of ketones with **3**–**5** at 0.05 mol-%.[a]

Complex	Ketone	Conversion [%]	[min]	TOF [h^{-1}]	*ee* [%]
3		97	1	3.0×10^5	
3		99	1	4.0×10^5	
3		94	10	2.8×10^5	
3		98	10	8.0×10^4	
4		96	1	3.0×10^5	85 (*S*)
5		97	2	2.3×10^5	83 (*R*)
4		96	1	2.9×10^5	89 (*S*)
4		96	2	2.5×10^5	94 (*S*)
4		98	5	1.5×10^5	90 (*S*)

[a] Ketone 0.1 M and NaOH 2 mol-% in 2-propanol at T = 82 °C.



Scheme 3. Formation of hydride ruthenium complexes.

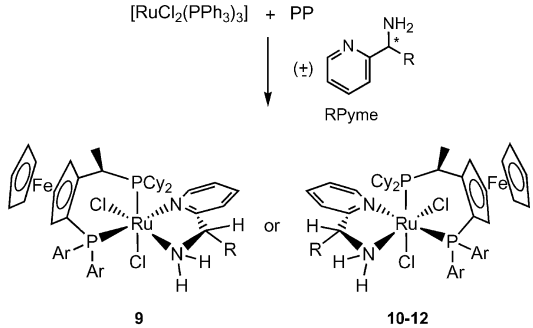
By contrast, the dihydride *cis*,*trans*-$[Ru(H)_2(PPh_3)_2(Pyme)]$ (**8**), prepared from the monohydride **6** and NaO*i*Pr, is catalytically active in the reduction of acetophenone without base (TOF = 5.5×10^3 h^{-1}) and addition of NaOH led to a notably higher rate (TOF = 1.1×10^4 h^{-1}). NMR stud-

ies showed that during the synthesis of **8**, the dihydride intermediate *cis*,*cis*-[Ru(H)$_2$(PPh$_3$)$_2$(Pyme)] (**7**) is formed and it slowly converts into the final product. This indicates that during catalysis the dichloride complexes [RuCl$_2$P$_2$(Pyme)] react with sodium isopropoxide, affording several hydride species, which are involved in the TH.

We want to point out that the complexes of the type [RuCl$_2$P$_2$(Pyme)] were reported independently by the groups of Morris et al. and Noyori et al., and were proven to be efficient catalysts for the HY of ketones. Thus, the compounds [RuXY(PPh$_3$)$_2$(Pyme)] (X, Y = H, Cl) and [RuHCl{(*S*)-tolbinap}(L)] [L = 1,1-dimethyl-1-(pyridin-2-yl)methanamine] display good catalytic activity in the hydrogenation of acetophenone in benzene and 2-propanol.[41] Conversely, [RuXY{(*S*)-tolbinap}(Pyme)] (X = Y = Cl and X = H, Y = BH$_4$) in ethanol are highly active catalysts for the asymmetric HY of bulky substrates, such as *t*Bu ketones, for which the related complexes *trans*-[RuCl$_2$(PP)(1,2-diamine)] show poor activity.[42] Therefore the development of the compounds [RuCl$_2$P$_2$(Pyme)] that are highly active in both TH and HY, by switching the reaction parameters, represents a significant step forward in the catalytic reduction of ketones.

A further improvement in the advance of asymmetric TH catalysts of this type was achieved with the isolation of the complexes *cis*-[RuCl$_2$(PP)(RPyme)] containing a chiral diphosphane PP correctly matched with a chiral 1-substituted Pyme (RPyme). With the well-known derivatives *trans*-[RuCl$_2$(PP)(1,2-diamine)], a higher level of enantioselectivity in the HY reactions was achieved using two matched chiral ligands. For these catalysts, the search of the suitable combination of the chiral ligands 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 auxiliary, leading to deactivation (chiral poisoning) or activation of one metal enantiomeric species.[43] Importantly, we found that a single diastereomer complex *cis*-[RuCl$_2$(PP)(RPyme)][44] can easily be obtained in high yield through a one-pot reaction of [RuCl$_2$(PPh$_3$)$_3$] with a chiral Josiphos diphosphane (PP) and two equivalents of a *racemic mixture* of RPyme[45] (R = alkyl, aryl), displaying a stereogenic carbon center bound to the active NH$_2$ function (Scheme 4).

Interestingly, these complexes catalyze the TH of methyl aryl ketones with very high rate and enantioselectivity (up to 99% *ee*) on account of the corrected combination of the PP and NN ligand pair. This represents the first example of an efficient asymmetric catalyst with two matched chiral ligands which is prepared without the necessity of using both ligands in enantiopure form. Complexes **9**–**12** (0.05 mol-%) display high catalytic activity in the asymmetric TH of methyl aryl ketones in 2-propanol at 60 °C and in the presence of NaO*i*Pr. The corresponding alcohols are formed quantitatively in 96–99% *ee* within a few minutes and with TOFs up to 7.0×10^4 h^{-1}, which, at this temperature, are among the highest values reported in the literature



	PP	Ar	R
9	(*R*,*S*)-Josiphos	Ph	Me
10	(*S*,*R*)-Josiphos	Ph	*t*Bu
11	(*S*,*R*)-Josiphos	4-OMe-3,5-Me$_2$C$_6$H$_2$	Me
12	(*S*,*R*)-Josiphos	4-OMe-3,5-Me$_2$C$_6$H$_2$	*t*Bu

Scheme 4. Synthesis of a single diastereomer complex [RuCl$_2$(PP)(RPyme)].

(Table 3). Experiments aimed to establish the matched/mismatched effect of the ligands show that when the single enantiomer (*R*)-MePyme is used with (*R*,*S*)-Josiphos, the substrate 2′-methoxyacetophenone is reduced to the (*R*)-alcohol with 71% *ee* (TOF = 1.5×10^4 h^{-1}), whereas with (*S*,*R*)-Josiphos, which leads to a single ruthenium diastereomer, the conversion to the (*S*)-alcohol occurs with both higher *ee* (98%) and rate (TOF = 3.2×10^4 h^{-1}).[44]

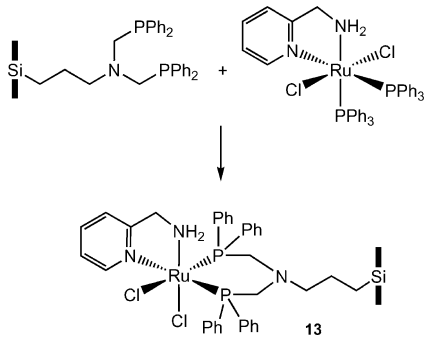
Table 3. Catalytic TH of methyl aryl ketones with **9**–**12** at 0.05 mol-%.[a]

Complex	Ar	Conversion [%]	[min]	TOF [h^{-1}]	*ee* [%]
9	Ph	97	5	6.3×10^4	96 (*R*)
9	3′-MeOC$_6$H$_4$	98	5	6.6×10^4	99 (*R*)
10	Ph	96	10	7.0×10^4	95 (*S*)
10	2′-ClC$_6$H$_4$	99	30	2.7×10^4	98 (*S*)
11	Ph	97	10	4.0×10^4	96 (*S*)
12	Ph	97	10	3.4×10^4	97 (*S*)
12	2′-MeOC$_6$H$_4$	98	30	2.5×10^4	98 (*S*)
12	3′-MeOC$_6$H$_4$	97	10	2.6×10^4	> 99 (*S*)

[a] Ketone 0.1 M and NaO*i*Pr 2 mol-% in 2-propanol at T = 60 °C.

Attempts were also made to prepare heterogeneous TH catalysts based on Pyme. The best results were obtained using a silica-immobilized complex of the type [RuCl$_2${RN(CH$_2$PPh$_2$)$_2$}(Pyme)] (**13**), prepared by reaction of *trans*,*cis*-[RuCl$_2$(PPh$_3$)$_2$(Pyme)] with a diphosphane covalently bound to silica, synthesized by reaction of a 3-aminopropyl-functionalized silica with formaldehyde and PHPh$_2$ [Equation (5)].[46]

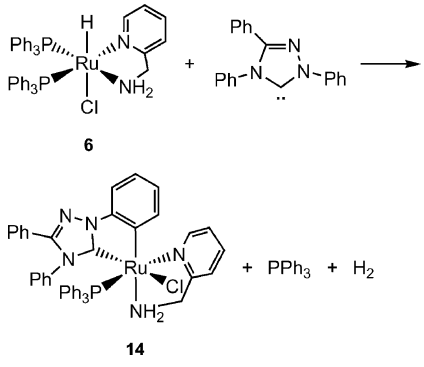
This system catalyzes the quantitative TH of acetophenone and it was possible to reuse this catalytic system for a second cycle. However, the efficiency of the catalyst considerably diminished in the successive reuses, indicating that the catalytically active ruthenium hydride species undergo deactivation.



(5)

4. A Carbene Pyme Ruthenium Complex

Heterocyclic carbene ligands have successfully been employed in homogeneous catalysis, on account of their favorable properties, such as low oxygen and thermal sensitivity, associated to a relatively strong bonding.[47] However, for the TH of carbonyl compounds only a few ruthenium catalysts based on carbene ligands have been reported.[48] With the aim to prepare catalysts which could associate the strong ligand acceleration effect of Pyme and high stability, we found that the monohydride *trans,cis*-[$RuHCl(PPh_3)_2$(Pyme)] (**6**) reacts straightforward with the commercially available free carbene 1,3,4-triphenyl-4,5-dihydro-1*H*-1,2,4-triazol-5-ylidene, affording the orthometalated ruthenium compound **14** [Equation (6)].[49]



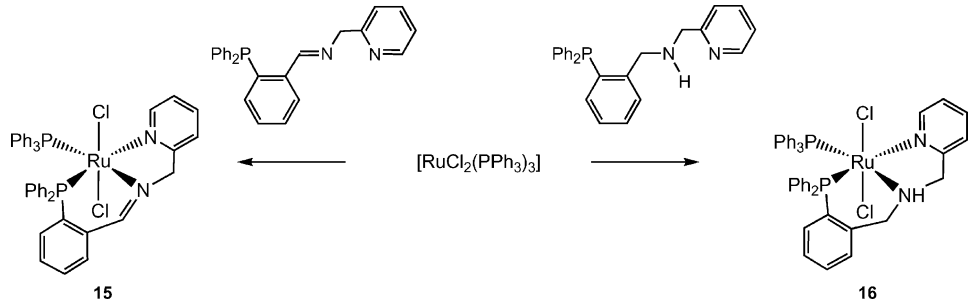
(6)

This complex in the presence of NaOH in 2-propanol at reflux is an efficient TH catalyst for the reduction of numerous substrates, namely alkyl aryl and dialkyl ketones, with TOF up to 1.2×10^5 h^{-1}, using 0.05 mol-% of catalyst. The comparison of the activity of the Pyme based catalysts here reported, showed that the mixed carbene phosphane **14** displays a higher rate than **6**, bearing two PPh_3, and its activity was only inferior to that of the diphosphane complexes *cis*-[$RuCl_2$(PP)(Pyme)]. Thus, the high activity of **14** may be ascribed to the presence of the strong orthometalated carbene ligand that retards the deactivation of the catalyst, a behavior observed also for the cyclometalated phosphane complex **2**.

5. PNN′ Pyme Ruthenium Complexes

The tridentate imino and amino complexes *trans*-[$RuCl_2(PPh_3)$(PNN′)] (**15**, **16**) were easily obtained by reaction of [$RuCl_2(PPh_3)_3$] with PNN′ ligands, prepared from Pyme and $Ph_2P(2\text{-}C_6H_4CHO)$, through displacement of PPh_3 (Scheme 5).[50]

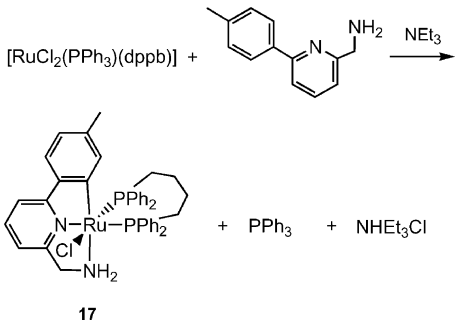
Compounds **15** and **16** (0.05 mol-%) in basic 2-propanol solution at reflux catalyze the transfer hydrogenation of different ketones with very high rate (TOF up to 2.5×10^5 h^{-1}). The corresponding imino and amino monohydride complexes *trans*-[$RuHCl(PPh_3)$(PNN′)] were prepared from *trans,cis*-[$RuHCl(PPh_3)_2$(Pyme)] (**6**) and the PNN′ ligands. Interestingly, under analogous experimental conditions, the imine and amine derivatives display the same catalytic activity, suggesting that during catalysis the imino precursors are converted into N-H amino species that are responsible for the high rate. The reduction of the C=N function of the coordinated ligand to the CH–NH moiety is favored by the excess of a strong base and at high temperature. In absence of base, the monohydride complexes *trans*-[$RuHCl(PPh_3)$(PNN′)] do not catalyze the reduction of acetophenone. With NaO*i*Pr their activity is lower (TOF up to 1.6×10^4 h^{-1}), compared to that of the dichloride precursors **15** and **16**, suggesting that different dihydride ruthenium isomers are involved in catalysis. By using PNN′ ligands with a CH_2CH_2 backbone connected to the pyridine ring, instead of one CH_2 group, 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 the TH.



Scheme 5. Synthesis of imino and amino complexes [$RuCl_2(PPh_3)$(PNN′)].

6. Terdentate CNN Ruthenium Complexes

To make asymmetric TH a valuable procedure alternative to HY, it is fundamental that the catalysts promote the reduction of the ketones with high rate and productivity, in addition to high enantioselectivity. Although different complexes are capable to catalyze the reduction of ketones with up 99% *ee*, the rates of non Pyme systems are generally lower than 10^4 h^{-1} and these catalysts necessitate of a relatively high loading ($\geq$ 0.01 mol-%) to achieve complete conversion of the substrate, because of their easy deactivation. With the aim to obtain both fast and robust catalytic systems, we have designed a ruthenium complex in which a diphosphane ligand is combined with a cyclometalated framework containing the Pyme motif. In this context, it is known that CN-orthometalated pyridine–ruthenium complexes can easily be prepared from 2-phenylpyridine and 6-phenyl-2,2′-bipyridine.[51] Thus, we found that 1-[6-(4-methylphenyl)pyridin-2-yl]methanamine, in which an aryl group is connected to the C atom in position 6 of Pyme, promptly reacts with the ruthenium precursor $[RuCl_2(PPh_3)(dppb)]$, leading to the orthometalated CNN pincer complex [RuCl(CNN)(dppb)] (**17**) [Equation (7)].[52]



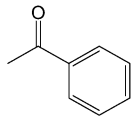
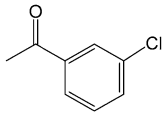
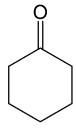
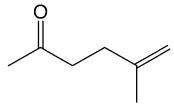
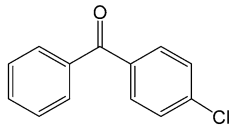
(7)

17

This compound displays an exceptionally high catalytic activity in the TH of ketones with 2-propanol in the presence of NaOH. As shown in Table 4, alkyl aryl, dialkyl and diaryl ketones were quantitatively and chemoselectively reduced to alcohols in a few minutes, using a low amount of **17** (0.005 mol-%) and affording TOFs up to 2.5×10^6 h^{-1}, which is the highest value reported in the literature.[18–21] The analogue of **17** displaying NMe_2 instead of NH_2 shows a poor activity, indicating that fast catalytic TH is assisted by the NH_2 functionality.

Importantly, with 0.001 mol-% of **17**, complete reduction of acetophenone was achieved in 1 h and experiments carried out at 5×10^{-4} mol-% of complex afforded a TON = 1.7×10^5. As example of application of this protocol, 1.97 g of the intermediate 4-chlorobenzhydrol (90% yield) was obtained from 4-chlorobenzophenone in 2 h using 0.076 mg of **17** (0.001 mol-%). Notably, only the system $[IrH_3(iPr_2PC_2H_4)_2NH]$ has been reported to promote the ketone TH at such low loading.[53] Complex **17** also catalyzes 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 (Table 5).[54]

Table 4. Catalytic TH of ketones with **17** at 0.005 mol-%.[a]

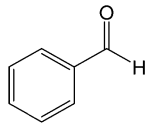
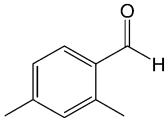
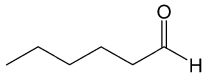
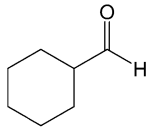
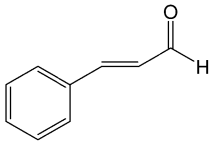
Ketone	Conversion [%]	[min]	TOF [h^{-1}]
	98	5	1.1×10^6
	99	1	2.5×10^6
	97	2	1.5×10^6
	97	5	7.0×10^5
	98	10	5.3×10^5

[a] Ketone 0.1 M and NaOH (2 mol-%) in 2-propanol at T = 82 °C.

The very short reaction time limits the side reactions (i.e. aldol condensation, catalyst deactivation via decarbonylation),[8] affording chemoselective TH of aldehydes. Thus, *trans*-cinnamaldehyde is quickly and quantitatively converted into cinnamyl alcohol in 30 s, whereas the reduction of the C=C double bond, affording 3-phenyl-1-propanol, requires hours. As extension to the asymmetric TH, we prepared CNN pincer ruthenium complexes containing chiral 1-(6-arylpyridin-2-yl)methanamines or diphosphane ligands. Preliminary results showed that the derivatives **18**[52b] and **19**[55] rapidly catalyze the asymmetric TH of methyl aryl ketones with up to 89% *ee*, using 0.005 mol-% of catalyst, a loading much lower than that commonly employed in the enantioselective TH of ketones (Figure 2).

The high performance of this catalytic system arises from the association of the robust cyclometalated ligand, containing the accelerating Pyme moiety, with the chelating diphosphane and consequently catalyst deactivation is significantly retarded. Therefore, these new CNN chiral ruthenium catalysts, which require a loading of 1/10 respect to that of the most efficient systems, represent a new significant improvement in the asymmetric TH of ketones, leading to a new standard for this reaction. This makes this procedure attractive from an industrial point of view and alternative to the well-establishes enantioselective HY reaction.

Table 5. Catalytic TH of aldehydes with **17** at 0.05 mol-%.[a]

Aldehyde	Conversion [%]	[s]	TOF [h^{-1}]
	99	30	3.0×10^5
	98	20	4.5×10^5
	99	30	3.0×10^5
	99	5 min[b]	2.0×10^5
	99	30	3.3×10^5

[a] Aldehyde 0.1 M and K_2CO_3 5 mol-% in 2-propanol at 82 °C. [b] **17** 0.01 mol-%.

7. Mechanism of the TH Mediated by Terdentate CNN Ruthenium Complexes

It is generally accepted that the role of the base in the catalytic TH is to generate a catalytically active M–H complex.[2b,56] Subsequent insertion of the ketone in the M–H leads to M-alkoxide species via an inner sphere mechanism.[40] For ruthenium complexes displaying a NH_2 functionality, an outer sphere mechanism, involving a Ru–H and a Ru-amide (the product of the delivery of a Ru–H hydride and a NH proton) has been proposed.[3] In this case, the formation of a Ru–OR complex bearing an amine NH_2 function has to be considered a nonproductive reaction and this species is regarded as catalytic reservoir of the metal amide.[3b] On account of the high control of the reactivity that CNN pincer ligands impose to the Ru center, the [RuCl(CNN)(PP)] system appears ideal for the investigation of elementary processes involved in the catalysis. Interestingly, we have found that reaction of **17** with sodium isopropoxide in a 2-propanol/hydrocarbon solutions afforded the alcohol adduct alkoxide [Ru(O*i*Pr)(CNN)(dppb)]·*n i*PrOH (**20**), and no Ru-amide species was detected (Scheme 6).[55]

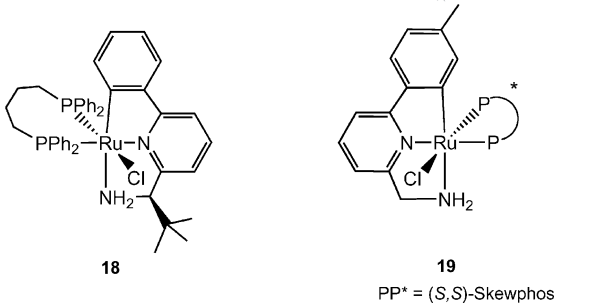
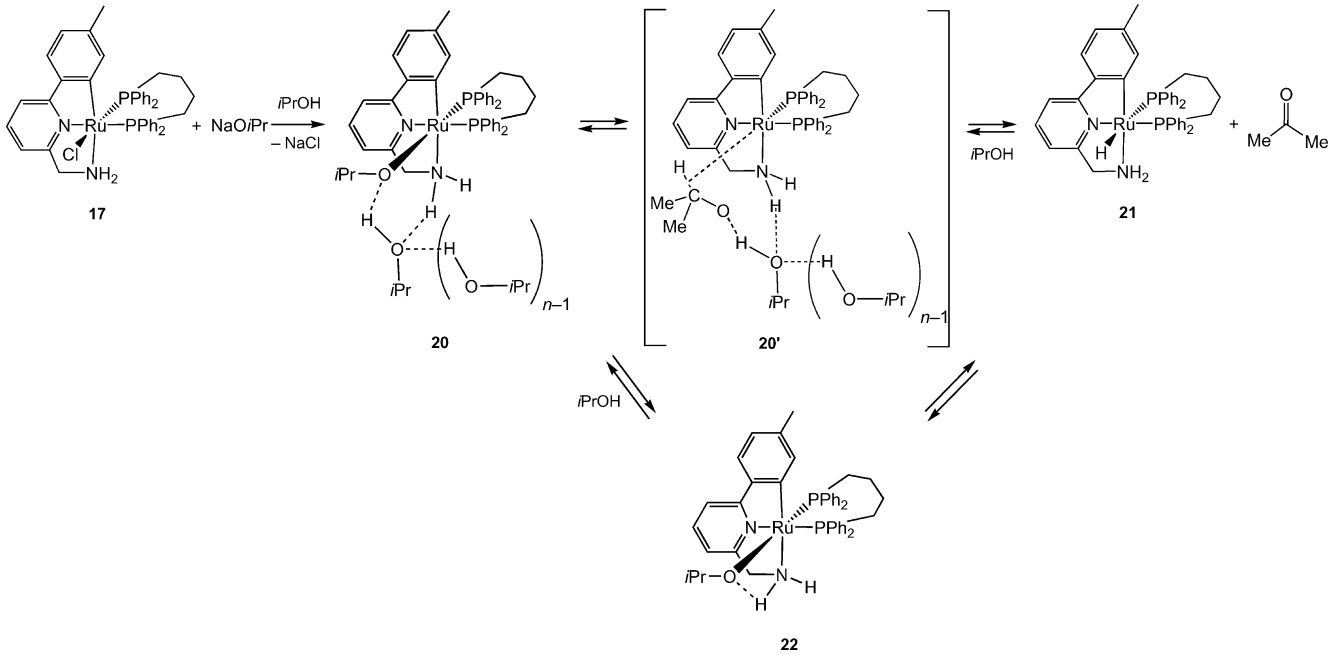


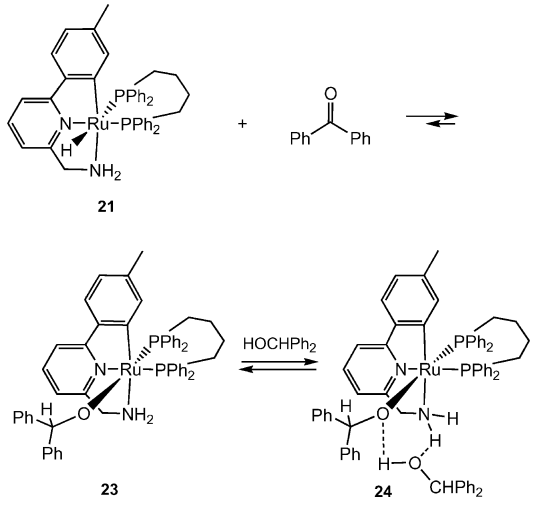
Figure 2. Chiral CNN Ru complexes.

NMR analysis in solution revealed a rapid equilibrium between the alkoxide **20** and the hydride **21**/acetone with an exchange rate of 5.4 ± 0.2 s^{-1} at 25 °C. In addition, the sim-



Scheme 6. Reversible β-hydrogen elimination from isopropoxide ruthenium complexes.

ple alkoxide **22**, which forms from the hydride **21** and acetone in absence of alcohol, equilibrates with **21** with a significant lower rate ($2.9 \pm 0.4\ s^{-1}$). We believe that the fast β-hydrogen elimination vs. acetone insertion occurs within a hydrogen bonding[57] network. The function of the $Ru–NH_2$ linkage is to promote an extensive hydrogen bonding with the solvent, thus lowering the energy of activation barriers. Following a concerted solvent-mediated mechanism for the TH, it is likely that the cleavage of the C–H bond occurs through decoordination and reorientation of the O*i*Pr ligand within the hydrogen bonding network with 2-propanol, namely via the species **20′** by a mixed inner/outer sphere mechanism (Scheme 6). Because the catalytic TH takes place in neat 2-propanol the concentration of **22** is negligible, respect to the alcohol adduct species **20**. Notably, a favorable influence of the alcohol in the β-hydrogen elimination from alkoxides and insertion of ketones into M–H bond was reported by different groups.[58] More recently, a mechanism involving an active role of the solvent in TH with a $Ru–NH_2$ system has been proposed by Handgraaf and Meijer.[59]



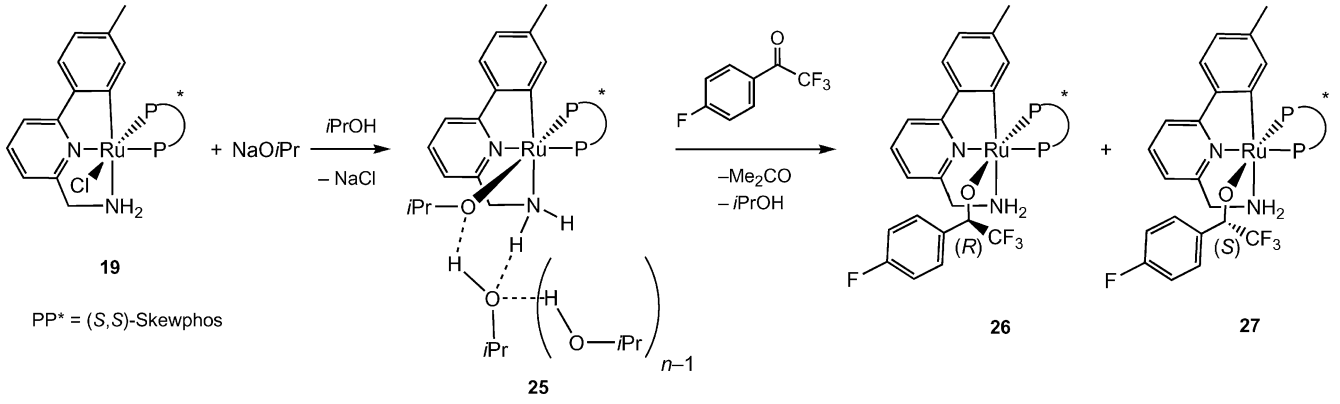
Scheme 7. Insertion of a Ph_2CO into the Ru–H bond and formation of an alcohol adduct alkoxide.

Isolable alkoxides were obtained with ketones containing electron-withdrawing groups for which the β-hydrogen-elimination is hindered. Reaction of the hydride **21** with benzophenone led to the corresponding alkoxide-amine complex **23**, which by addition of benzhydrol afforded the alcohol adduct **24** which rapidly equilibrates with **23** (Scheme 7).[52b]

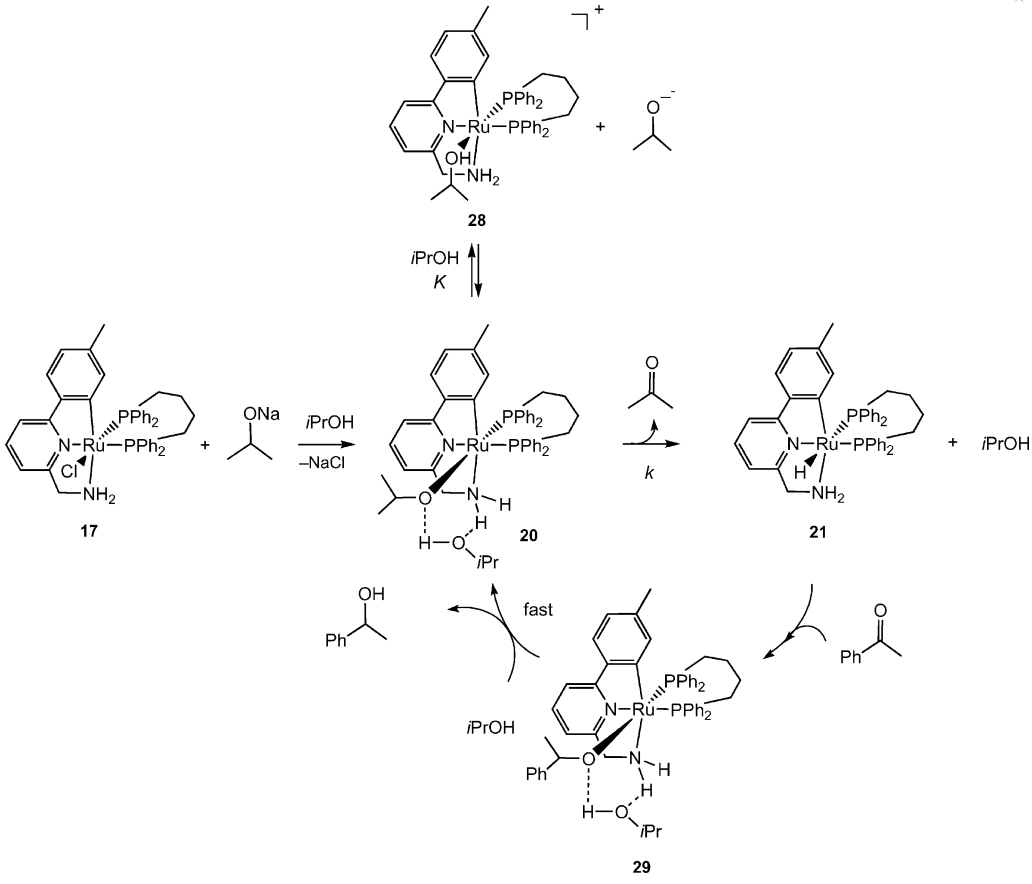
Further evidence of the involvement of alkoxide ruthenium species in the catalytic TH was provided by the chiral CNN complex **19**, containing the (*S*,*S*)-Skewphos diphosphane, which catalyzes the reduction of the prochiral ketone $CF_3CO(4\text{-}C_6H_4F)$ with 64% *ee*. The alcohol adduct alkoxide **25**, obtained from **19** and NaO*i*Pr in 2-propanol, rapidly equilibrates with the corresponding Ru-hydride with elimination of acetone, as observed for the species **20**. Interestingly, reaction of **25** with $CF_3CO(4\text{-}C_6H_4F)$ affords a mixture of the diastereomer alkoxides [Ru{OCH(CF_3)(4-C_6H_4F)}(CNN){(*S*,*S*)-Skewphos}] (**26/27**) with 67% *de* (Scheme 8).[55]

This value is much the same as the *ee* of the alcohol (*R*)-$CF_3CH(OH)(4\text{-}C_6H_4F)$ formed in catalysis with **19**, indicating that CNN ruthenium alkoxides with the NH_2 functionality are species involved in the catalytic asymmetric TH. Kinetic studies on the role of the base in the TH of acetophenone catalyzed by **17** in 2-propanol are consistent with the involvement of ruthenium hydride and alkoxide species, and a proposed catalytic cycle is depicted in the Scheme 9.[60]

The chloride **17** reacts with NaO*i*Pr in 2-propanol, leading to the isopropoxide **20** stabilized by the alcohol. This species rapidly equilibrates with the cationic alcohol adduct **28** (catalyst reservoir) with a pre-equilibrium constant of about $K \approx 2 \times 10^{-5}$ M. Complex **20** undergoes a β-hydrogen elimination affording the hydride **21** which reacts with acetophenone, leading to the alcohol adduct alkoxide **29**. In the final step this species rapidly reacts with 2-propanol (in excess), affording 1-phenylethanol and **20** that closes the cycle. The formation of **21** from **20** is likely to be rate-determining step of the catalytic transfer hydrogenation, in which **20** is the predominant species. The activation parameters are $\Delta H^{\ddagger} = 14.0 \pm 0.2$ kcal/mol and $\Delta S^{\ddagger} = -3.2 \pm 0.5$



Scheme 8. Formation of diastereomer alkoxide ruthenium complexes.



Scheme 9. Proposed catalytic cycle of the TH of PhCOMe.

eu and the latter low value suggests that no substantial rearrangement occurs in the rate-determining step. This is in agreement with an intramolecular conversion of alcohol adduct alkoxide **20** into the hydride **21**, through a cleavage of the C–H bond within a hydrogen bonding network promoted by the Ru-NH_2 functionality.

8. Summary and Outlook

The discovery that 1-(pyridin-2-yl)methanamine (Pyme) based phosphane ruthenium complexes show a remarkably high catalytic activity in the transfer hydrogenation (TH) of ketones has allowed the designing of a new family of fast and highly productive catalysts for the synthesis of alcohols. The rate for the reduction of acetophenone has progressively increased from $6.0 \times 10^4\ h^{-1}$ for the cyclometalated [RuCl{(2-CH_2-6-MeC_6H_3)PPh_2}(CO)(Pyme)] (**2**) to $1.1 \times 10^6\ h^{-1}$ for the CNN pincer complex [RuCl(CNN)(dppb)] (**17**) which can be used at 0.001 mol-%. This catalyst is the most active system reported in the literature. High enantioselectivity (up to 99% *ee*) has been achieved with the structurally well defined complexes [$RuCl_2$(Josiphos)(RPyme)], obtained from a chiral diphosphane (Josiphos) and a racemic mixture of 1-substituted Pyme ligands, through a diastereoselective reaction. The high performance of the achiral and chiral pincer complexes [RuCl(CNN)(PP)] (PP = diphosphane), which display TOF values up to $2.5 \times 10^6\ h^{-1}$ and can be employed at loadings of as low as 0.001 mol-%, holds promise for the application of these catalysts in an industrial context, being complementary to the well-established hydrogenation (HY), avoiding the use of dihydrogen under pressure. The investigations of the elementary steps of the C–H bond activation reaction led to a mixed inner/outer sphere mechanism for the TH involving Ru-H and Ru-OR species. In the β-hydrogen elimination the crucial role of the NH_2 function is to promote a hydrogen bonding network with 2-propanol. These finding can help to conceive new experiments for elucidating the fundamental paths of TH and thus improving the efficiency of the catalysis through an appropriate choice of the reaction parameters. Very recently the extension of this chemistry to osmium, surprisingly led to efficient asymmetric TH and HY catalysts,[61] revealing the potentiality of the Pyme based ligands for other metals and allowing a broad scope.

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