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Role of the NH_2 Functionality and Solvent in Terdentate CNN Alkoxide Ruthenium Complexes for the Fast Transfer Hydrogenation of Ketones in 2-Propanol

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Abstract: The reaction of [RuCl(CNN)(dppb)] (**1**; HCNN = 6-(4-methylphenyl)-2-pyridylmethylamine) with NaO*i*Pr in 2-propanol/C_6D_6 affords the alcohol adduct alkoxide [Ru(O*i*Pr)(CNN)(dppb)]·*n i*PrOH (**5**), containing the Ru–NH_2 linkage. The alkoxide [Ru(O*i*Pr)(CNN)(dppb)] (**4**) is formed by treatment of the hydride [Ru(H)(CNN)(dppb)] (**2**) with acetone in C_6D_6. Complex **5** in 2-propanol/C_6D_6 equilibrates quickly with hydride **2** and acetone with an exchange rate of $(5.4 \pm 0.2)\ s^{-1}$ at 25 °C, higher than that found between **4** and **2** ($(2.9 \pm 0.4)\ s^{-1}$). This fast process, involving a β-hydrogen elimination versus ketone insertion into the Ru–H bond, occurs within a hydrogen-bonding network favored by the Ru–NH_2 motif. The cationic alcohol complex [Ru(CNN)(dppb)(*i*PrOH)](BAr^f_4) (**6**; Ar^f = 3,5-$C_6H_3(CF_3)_2$), obtained from **1**, Na[BAr^f_4], and 2-propanol, reacts with NaO*i*Pr to afford **5**. Complex **5** reacts with either 4,4′-difluorobenzophenone through hydride **2** or with 4,4′-difluorobenzhydrol through protonation, affording the alkoxide [Ru{OCH(4-$C_6H_4F)_2$}(CNN)(dppb)] (**7**) in 90 and 85 % yield of the isolated product. The chiral CNN–ruthenium compound [RuCl(CNN){(*S*,*S*)-Skewphos}] (**8**), obtained by the reaction of [$RuCl_2(PPh_3)_3$] with (*S*,*S*)-Skewphos and orthometalation of HCNN in the presence of NEt_3, is a highly active catalyst for the enantioselective transfer hydrogenation of methylaryl ketones (turnover frequencies (TOFs) of up to $1.4 \times 10^6\ h^{-1}$ at reflux were obtained) with up to 89 % *ee*. Also the ketone $CF_3CO(4\text{-}C_6H_4F)$, containing the strong electron-withdrawing CF_3 group, is reduced to the *R* alcohol with 64 % *ee* and a TOF of $1.5 \times 10^4\ h^{-1}$. The chiral alkoxide [Ru(O*i*Pr)(CNN){(*S*,*S*)-Skewphos}]·*n i*PrOH (**9**), obtained from **8** and NaO*i*Pr in the presence of 2-propanol, reacts with $CF_3CO(4\text{-}C_6H_4F)$ to afford a mixture of the diastereomer alkoxides [Ru{OCH(CF_3)(4-C_6H_4F)}(CNN){(*S*,*S*)-Skewphos}] (**10**/**11**; 74 % yield) with 67 % *de*. This value is very close to the enantiomeric excess of the alcohol (*R*)-$CF_3CH(OH)(4\text{-}C_6H_4F)$ formed in catalysis, thus suggesting that diastereoisomeric alkoxides with the Ru–NH_2 linkage are key species in the catalytic asymmetric transfer hydrogenation reaction.

Keywords: alkoxides · asymmetric catalysis · hydrogen transfer · ruthenium · solvent effects

Introduction

The catalytic transfer hydrogenation of carbonyl compounds has been recognized over the last decade as a practical methodology for the preparation of alcohols.[1] Ruthenium complexes have been successfully employed in the asymmetric reduction of ketones using 2-propanol (or formic acid) as a hydrogen source. Particular attention has been devoted to the catalysts, containing the Ru–NH_2 linkage, developed by Noyori and co-workers which offer high performance in terms of rate and enantioselectivity (bifunctional catalysis).[2] In the absence of acidic NH_2 (OH) protons, it is generally assumed that transition-metal-catalyzed transfer hydrogenation occurs via a metal hydride and alkoxide species (the product of the ketone insertion into M–H bond) through an inner-sphere mechanism.[3] To account for the crucial role of the amine NH_2 function in enhancing the activity of Ru complexes, an outer-sphere mechanism, involving a Ru–hydride and a Ru–amide (the product of the delivery of a Ru–H hydride and N–H proton) has been proposed.[2a] In this case, the formation of a ruthenium–alkoxide complex bearing an amine NH_2 function has to be consid-

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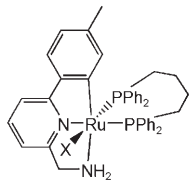
ered as a nonproductive reaction, and this species is regarded as a catalytic reservoir of the metal amide.[2a] Recently, a new mechanism involving an active role of the solvent, with the substrate appearing as an alkoxide-like intermediate, has been proposed by Handgraaf and Meijer for a Ru–NH_2 system on the basis of an ab initio molecular dynamics study.[4]

As regards to the properties of the transition-metal alkoxides, it is well known that these species, characterized by a strongly polarized M–O bond, are extremely reactive toward protic compounds.[5] The reaction with alcohols readily leads to an alkoxide exchange, possibly through the formation of an alcohol adduct stabilized by M–O···H–O hydrogen bonding[6] followed by proton transfer. Fast alkoxide displacement on the NMR chemical-shift timescale (<1 s)[7] has been observed for alkaline and early transition-metal compounds.[5a] For late-transition-metal species, a fast exchange has been reported for Pd^{II} complexes bearing ligands with a strong *trans* influence with respect to the M–O bond[8] and for a Cp*Ir^{III} complex (Cp* = 1,2,3,4,5-pentamethylcyclopentadienyl) containing an amine NH_2 function.[9] A second important feature of late-transition-metal alkoxides is the low stability toward thermal decomposition,[10] thus providing one of the most practical approaches to the synthesis of metal hydrides (for example, through a β-hydrogen elimination pathway).[5c,11] The reverse reaction, that is, the insertion of a ketone into a M–H bond, has been described for ketones containing electron-withdrawing groups and strongly hydridic hydrides.[12]

Recently, we reported that the terdentate CNN compound [RuCl(CNN)(dppb)] (**1**; HCNN = 6-(4-methylphenyl)-2-pyridylmethylamine, dppb = bis(diphenylphosphino)butane) with a NH_2 function promotes the transfer hydrogenation of ketones and aldehydes in basic 2-propanol at reflux in a remarkably high rate (TOF[13] values were up to 2.5×10^6 h^{-1}.[14]



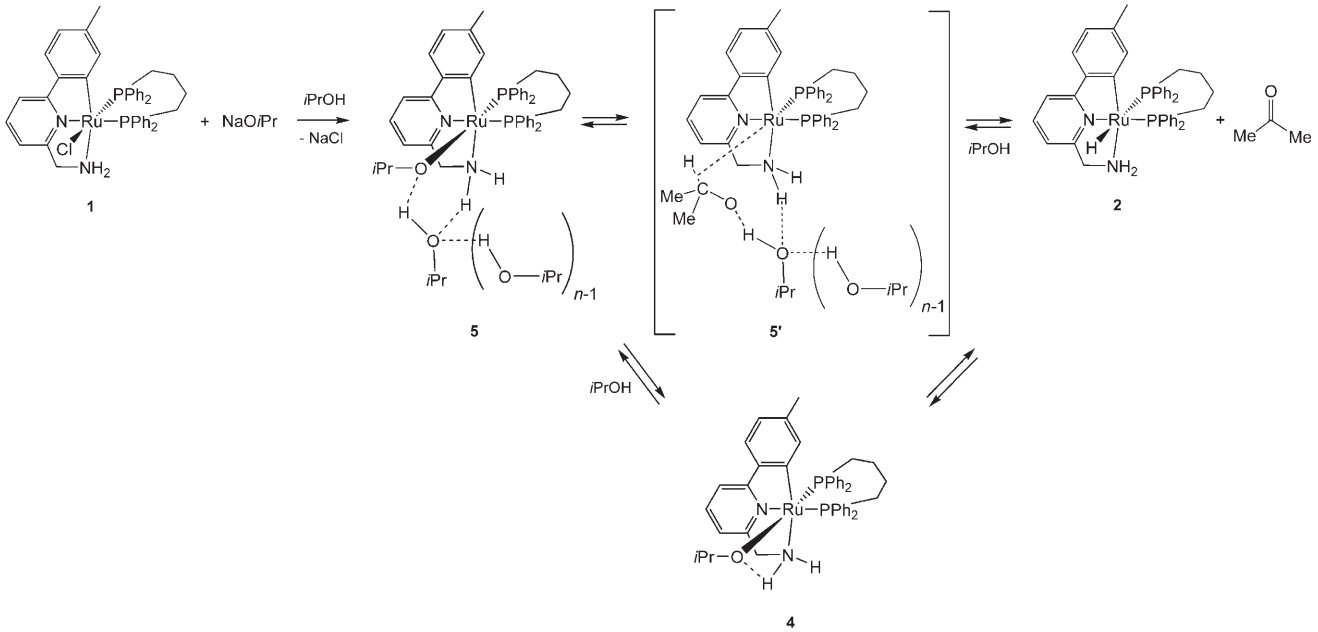
X = Cl (**1**), H (**2**), $OCHPh_2$ (**3**)

Kinetic and NMR studies of **1** in basic 2-propanol suggest that hydride [Ru(H)(CNN)(dppb)] (**2**) and Ru–alkoxides are key species in the catalytic cycle and that the solvent may actively take part in the reaction.[14b,c] The isolation of the alkoxide–amine species [Ru($OCHPh_2$)(CNN)(dppb)] (**3**) from **2** and Ph_2CO, instead of the amide, indicates that the coordinated primary amine displays a relatively weak acidity.[14a]

We present herein experimental evidence that the solvent and NH_2 function play an active role in enhancing the rate of the transfer hydrogenation reaction in terdentate CNN ruthenium complexes. Thus, the alcohol adduct Ru–alkoxide [Ru(O*i*Pr)(CNN)(dppb)]·*n* *i*PrOH, which forms from **1** and NaO*i*Pr in 2-propanol, rapidly equilibrates with hydride **2** and acetone through an alkoxide–alcohol hydrogen-bonding network favored by the Ru–NH_2 linkage. When a chiral ruthenium complex is used, the catalytic asymmetric transfer hydrogenation reaction has been proven to occur via diastereomeric Ru–alkoxide intermediates.

Results and Discussion

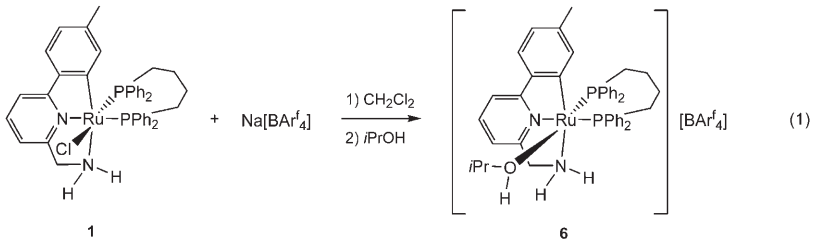
NMR spectroscopic studies on the Ru–O*i*Pr/Ru–H system: The reaction of **1** with NaO*i*Pr in a 2-propanol/C_6D_6 mixture leads to substitution of the chloride ligand with isopropoxide. This reaction affords alcohol adduct alkoxide **4**·*n* *i*PrOH (**5**), which is in equilibrium with hydride **2**, as inferred from NMR spectroscopic analysis (Scheme 1).



Scheme 1. Formation of ruthenium isopropoxides **4** and **5** and hydride **2**.

Alternatively, **5** is formed by the treatment of a suspension of **2** in 2-propanol/C_6D_6 with acetone (Scheme 1). When **2** is allowed to react with acetone in [D_6]benzene and in the absence of 2-propanol, the ^{31}P NMR spectrum of the solution reveals the formation of the simple isopropoxide **4**. Two doublets at $\delta = 55.5$ (P atom *trans* to the O*i*Pr group) and 37.8 ppm ($^2J(P,P) = 34.0$ Hz), which are values close to those of the analogous alkoxide **3** ($\delta = 57.0$ and 37.3 ppm with $^2J(P,P) = 34.2$ Hz), are displayed (Scheme 1).[14b] In the ^1H NMR spectrum, **4** shows a broad downfield signal for one NH_2 proton ($\delta = 4.32$ ppm), whereas the resonance of the OCH group is at $\delta = 3.69$ ppm. Extensive NMR spectroscopic measurements in solution reveal a complex behavior for the alkoxides **4**/**5**, which involve: 1) hydrogen bonding with 2-propanol and 2) the reversible formation of the ruthenium hydride [Ru(H)(CNN)(dppb)] (**2**). Thus, the addition of 2-propanol to a solution of **4** in C_6D_6 leads to the alcohol adduct **5** (Scheme 1), possibly involving a six-membered RuO···HO(R)···HN cycle, as observed for the related complexes *trans*-[Ru(H)(OPh)($H_2NCMe_2CMe_2NH_2$)(PPh_3)$_2$]·PhOH and [Ru{$OC(CF_3)_2CH_2NH_2$}$_2$(CO)$_2$]·2CH_3OH in the solid state.[15]

With ten equivalents of *i*PrOH, the ^{31}P NMR spectrum of **5** displays two doublets at $\delta = 54.3$ and 43.5 ppm ($^2J(P,P) = 34.0$ Hz), the latter signal gradually shifts up to $\delta = 46$ ppm by further addition of 2-propanol. The same behavior is observed when different alcohols of similar acidity, such as ethanol or 1-phenylethanol, are added to **4** or **5**, thus suggesting that **5** is stabilized by a hydrogen-bonding network in which a fast alcohol exchange occurs. A ^1H–^1H COSY experiment carried out on **5** in C_6D_6 with 2-propanol (30 equiv) enables the identification of two signals for the amine NH_2 group at $\delta = 3.52$ and 1.75 ppm coupled with the protons of the NCH_2 group ($\delta = 3.87$ and 3.30 ppm), whereas no signals for an NH amide species could be observed. In addition to the signals for 2-propanol, no resonances for the isopropoxide ligand were observed, thus indicating that the ligand O*i*Pr, the hydrogen-bonded *i*PrOH, and free *i*PrOH quickly exchange on the NMR timescale in **5**. The ^1H NMR spectroscopic data of the isolated amine–alkoxide [Ru($OCHPh_2$)(CNN)(dppb)] (**3**) suggest an intramolecular O···HN hydrogen bond between the NH_2 moiety and OR ligand,[14a] in agreement with theoretical calculations on related ruthenium complexes.[2a,16] The addition of Ph_2CHOH to **3** affords the alcohol adduct **3**·*n*Ph_2CHOH, in which the ligand $OCHPh_2$ and Ph_2CHOH are in fast exchange (70 ms).[14b] Although ruthenium complexes containing a coordinated alcohol group have been reported,[17] species **5** is better regarded as an alcohol adduct Ru–alkoxide [Ru(OR)L_m]·*n*ROH and not as the ion-pair alcohol complex [Ru(ROH)L_m]$^+$[(OR)(ROH)$_{n-1}$]$^-$.[17a,b] As a matter of fact, the cationic alcohol complex [Ru(CNN)(dppb)(*i*PrOH)](BAr$^f_4$) (**6**; Ar^f = 3,5-$C_6H_3(CF_3)_2$), can be readily prepared from **1** and Na(BAr$^f_4$) in dichloromethane followed by treatment with 2-propanol [Eq. (1)].



(1)

Complex **6** shows a weakly coordinated 2-propanol molecule, as inferred from ^1H and ^{31}P NMR spectroscopic analysis (C_6D_6), which promptly reacts with one equivalent of NaO*i*Pr in *i*PrOH to afford **5** by substitution (or deprotonation) of the *i*PrOH ligand.

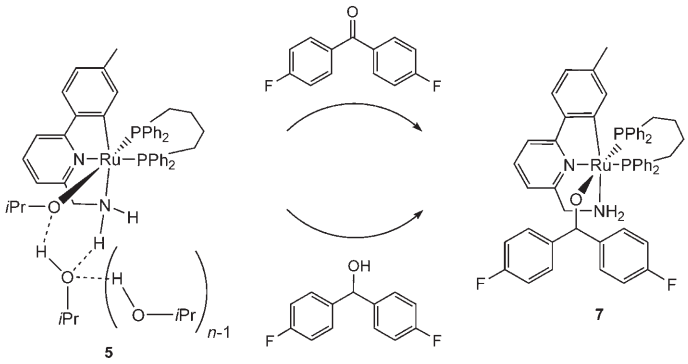
Interestingly, alkoxides **4** and **5** rapidly equilibrate at room temperature with hydride **2** with elimination of acetone (Scheme 1). The ^{31}P NMR spectroscopic measurements in 2-propanol/C_6D_6 (1:1, v/v) show that **5** is relatively stable relative to **2**/acetone and the equilibrium of **5** versus **2**/acetone shifts to the hydride ($K \times 10^3 = 3.2$, 5.6, and 9.5 M at 50, 60, and 70 °C, respectively) upon heating.[18] The ^{31}P–^{31}P NOESY experiments carried out on mixtures containing alkoxides **4**, **5**, and hydride **2** ($\delta = 65.7$ and 34.6 ppm; P atom *trans* to the hydride; $^2J(P,P) = 17.2$ Hz) in 2-propanol/C_6D_6 allowed us to determine the rates of the exchange processes involving the three species. The apparent global constant for the exchange between the two alkoxides **4** and **5** is (1.8 ± 0.2) s^{-1} at 25 °C. Importantly, the rate of exchange between alcohol adduct **5** and hydride **2** is (5.4 ± 0.2) s^{-1}, which is higher relative to the rate measured for the conversion of **4** into **2** ((2.9 ± 0.4) s^{-1}). This rate should be only partially affected by spin diffusion, because a nearly identical value is determined at a low alcohol concentration ((2.8 ± 0.1) s^{-1}).

It should be pointed out that in the catalytic process, which occurs with 2-propanol as the solvent, the concentration of **4** is negligible, whereas **5** is the key species involved in both the alkoxide–alcohol exchange and the C–H bond-cleavage reactions. These data clearly indicate that the alcohol moiety plays an active role in accelerating the β-hydrogen elimination versus the ketone insertion reaction, which can be ascribed to the hydrogen-bonding network involving the Ru–alkoxide and Ru–NH_2 function. An increase in the β-hydrogen elimination rate upon the addition of alcohol was observed by Blum and Milstein for Ir–alkoxides,[11e] and a mechanism involving a hydrogen-bonding network was proposed.[19] Fast insertion of carbonyl compounds into W–H and Re–H bonds mediated by proton sources was reported by Jacobsen and Berke.[20] In addition, a remarkable influence of the ratio of 2-propanol/benzene on the rate of the transfer hydrogenation of imines induced by the Shvo catalyst has been described by Samec and Bäckvall.[21]

A comparison of the behavior of **1** with the analogous complex containing an NMe_2 function instead of an NH_2 function shows that the latter is poorly active in transfer hydrogenation. The reaction with NaO*i*Pr in *i*PrOH gives a species that is analogous to **4** (but not **5**) and unstable with respect to β-hydrogen elimination, thus slowly affording the corresponding Ru–hydride (timescale = hours).[14b] These results clearly indicate that the amine NH_2 group in combination with 2-propanol plays both a thermodynamic and a kinetic role in 1) stabilizing alcohol adduct **5** versus hydride **2** and 2) increasing the rate of β-hydrogen elimination versus the ketone insertion reaction. According to the concerted solvent-mediated mechanism for transfer hydrogenation within a Ru–NH_2 system,[4] 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 in the case of 2-propanol, namely, via the species **5′** by a mixed inner-/outer-sphere mechanism (Scheme 1). The concomitant presence in **5** of a phosphane *trans*[22] to the OR ligand and Ru(OR)···HOR hydrogen bonding may lead to a weak and highly polarized Ru–OR bond. The crucial role of the amine NH_2 function may be ascribed to its ability to promote extensive hydrogen bonding with the solvent, thus lowering the energy barriers in a manner similar to the cooperative effect of enzymes.[23] The insertion of acetone into the Ru–H bond should occur through the reverse pathway and entails hydrogen bonding between 2-propanol and the ketone.[24]

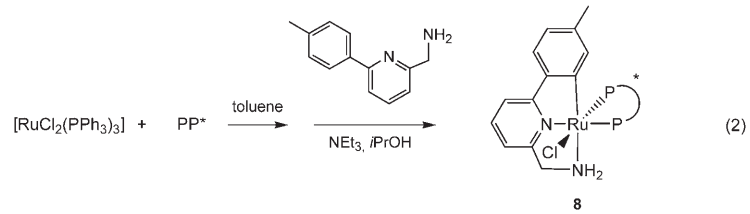
Isolation of Ru–alkoxide complexes: The fast alkoxide–hydride equilibrium reported herein suggests that isopropoxide **5** should promptly react with carbonyl compounds through the elimination of acetone, a reaction that has been sparingly described.[25] Thus, fluoro-substituted alkoxide **7** can be readily prepared by the treatment of **5** with 4,4′-difluorobenzophenone in a mixture of 2-propanol/toluene at room temperature (90% yield; Scheme 2).

Alternatively, **7** has also been isolated starting from hydride **2** and a ketone (90% yield). A further route to obtain **7** entails the protonation of **5** with the alcohol 4,4′-difluorobenzhydrol in 2-propanol/toluene (85% yield; Scheme 2). It is worth noting that the presence of electron-withdrawing groups in the alkoxide ligand stabilizes **7** with respect to β-hydrogen elimination. The ^{19}F NMR spectrum of **7** in C_6D_6 shows two singlets ($\delta = -119.5$ and -120.0 ppm) for two nonequivalent C_6H_4F groups, which disappear through the addition of alcohols, thus leading to a broad signal close to that of free 4,4′-difluorobenzhydrol ($\delta = -116.2$ ppm) and indicating a rapid alkoxide–alcohol exchange on the NMR timescale similar to alcohol adduct **5**. Complex **7** reacts with benzophenone at room temperature in C_6D_6, thus leading to an equilibrium reaction in which **3** is formed by the elimination of 4,4′-difluorobenzophenone (timescale = hours). The addition of alcohols (4,4′-difluorobenzhydrol or *t*BuOH) results in faster equilibration through the formation of alcohol adducts, thus indicating that the presence of protic compounds increases the rate of the reaction.

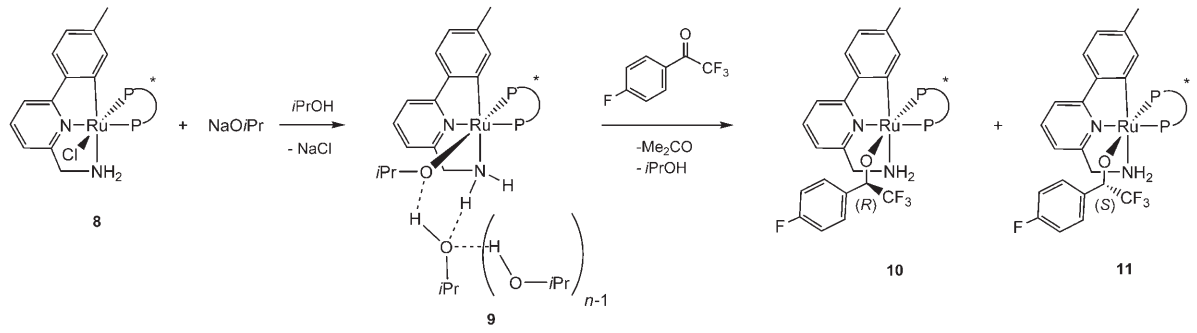


Scheme 2. Syntheses of the alkoxide **7** by reaction of **5** with a ketone or alcohol.

Apparently, the asymmetric transfer hydrogenation of ketones catalyzed by chiral terdentate CNN ruthenium complexes [RuCl(CNN)(PP)] (PP = diphosphane) involves the formation of diastereomeric Ru–alkoxide species. It is worth noting that Daley and Bergens[12a] reported the characterization of diastereomeric Ru–alkoxide species that are intermediates in the enantioselective hydrogenation of ketones. In contrast, no examples of Ru–OR species in an asymmetric transfer hydrogenation reaction have been described. Following the procedure for the synthesis of **1**,[14a] the chiral CNN ruthenium complex [RuCl(CNN){(*S*,*S*)-Skewphos}] (**8**) was obtained in 75% yield by reaction of $[RuCl_2(PPh_3)_3]$ with (*S*,*S*)-Skewphos at 110 °C in toluene (2 h) and the subsequent orthometalation of 6-(4-methylphenyl)-2-pyridylmethylamine with NEt_3 in 2-propanol at reflux (2 h) [Eq. (2)].



Compound **8** (0.05 mol%) is a highly active catalyst for the asymmetric transfer hydrogenation of different ketones in 2-propanol with NaO*i*Pr (2 mol%). The substrate $CH_3CO(2\text{-}C_6H_4Cl)$ was quantitatively reduced at 82 °C in 4 min to the *S* alcohol with 76% *ee* and a remarkable high TOF of $1.4 \times 10^6\ h^{-1}$. The substrates CH_3COPh, $CH_3CO(2\text{-}C_6H_4Cl)$, and $CH_3CO(3\text{-}C_6H_4Cl)$ were reduced at 60 °C into the corresponding *S* alcohols with 78, 80, and 89% *ee*, respectively, in less than 30 min (98–99% conversion) with TOFs of 1.3–$1.4 \times 10^5\ h^{-1}$. The fluoro derivative $CF_3CO(4\text{-}C_6H_4F)$ quantitatively led to the *R* alcohol with 64% *ee* in 30 min at 60 °C



Scheme 3. Formation of isopropoxide **9** and diastereomeric alkoxides **10**/**11**.

(0.5 mol% of **8** and TOF = 1.5×10^4 h^{-1}). Interestingly, we succeeded in the isolation of the corresponding diastereomeric Ru–alkoxide intermediates starting from **8** and $CF_3CO(4\text{-}C_6H_4F)$, which contained the strong electron-withdrawing CF_3 group. Treatment of **8** with NaO*i*Pr in C_6D_6 or toluene in the presence of 2-propanol readily afforded the alcohol adduct Ru–alkoxide [Ru(O*i*Pr)(CNN){(*S*,*S*)-Skewphos}]·*n i*PrOH (**9**), whose $^{31}P\{^1H\}$ NMR spectrum shows two doublets at $\delta = 65.6$ and 50.4 ppm ($^2J(P,P) = 43.3$ Hz) in C_6D_6 (Scheme 3).[26]

A rapid exchange between O*i*Pr and *i*PrOH occurs in **9**, as inferred from ^1H and ^{13}C NMR spectroscopic analysis, according to the behavior of **5**. The reaction of chiral isopropoxide **9** with one equivalent of $CF_3CO(4\text{-}C_6H_4F)$ in 2-propanol/toluene rapidly leads to the complete reduction of the ketone, as inferred from ^{19}F NMR spectroscopic analysis. The elimination of 2-propanol affords the isolation of a mixture of the diastereomeric alkoxides [Ru{OCH(CF_3)(4-C_6H_4F)}(CNN){(*S*,*S*)-Skewphos}] (**10**/**11**; 74% yield) in a 5:1 molar ratio (67% *de*), as inferred from NMR spectroscopic analysis. The ^{19}F NMR spectrum shows two singlets at $\delta = -76.3$ and -77.0 ppm for the CF_3 group of **10** and **11**, respectively, whereas the ^{31}P NMR doublets at $\delta = 66.7$ and 45.0 ppm ($^2J(P,P) = 44.7$ Hz) are for **10** and those at $\delta = 67.0$ and 44.7 ppm ($^2J(P,P) = 44.6$ Hz) are for **11**. The ^1H NMR spectrum of **10**/**11** shows a quartet of doublets at $\delta = 4.17$ ppm ($^3J(H,F) = 7.4$, $^4J(H,P) = 3.2$ Hz) for the OCH moiety of the major complex **10**, whereas the $^{13}C\{^1H\}$ NMR signal for OCH is at $\delta = 77.4$ ppm ($^2J(C,F) = 27.6$ Hz), which is shifted downfield relative to the free alcohol ($\delta = 72.2$ ppm). The protonation of **10**/**11** with acetic acid affords the alcohol (*R*)-$CF_3CH(OH)(4\text{-}C_6H_4F)$ with 66% *ee*, which is much the same as the *de* value of **10**/**11** and is close to the *ee* value (64%) of the *R* alcohol obtained in the catalytic transfer hydrogenation reaction with **8**. Therefore, these results indicate that diastereomeric ruthenium–alkoxides are key species in the fast catalytic asymmetric transfer hydrogenation of ketones promoted by Ru–NH_2 systems.

Conclusion

In conclusion, we have reported herein experimental evidence that in terdentate CNN ruthenium complexes the crucial role of the Ru–NH_2 function in enhancing the rate of the catalytic transfer hydrogenation of ketones is ascribed to its ability to form a hydrogen-bonding network with 2-propanol and alkoxides, thus leading to the alcohol adducts [Ru(O*i*Pr)(CNN)(PP)]·*n i*PrOH. These labile species equilibrate quickly with the hydrides [Ru(H)(CNN)(PP)] and react with ketones to afford ruthenium–alkoxides through a route in which the solvent takes an active role. When chiral ruthenium complexes are employed, diastereomeric alkoxides are formed, and these species have been proven to be key intermediates in the catalytic enantioselective reduction of ketones.

Experimental Section

General: All the reactions were carried out under argon using standard Schlenk techniques. The solvents were carefully dried by standard methods and distilled under argon before use. Compounds **1**,[14a] **2**,[14a] [$RuCl_2(PPh_3)_3$],[27] and $Na(BAr^f_4)$[28] were prepared according to reported procedures, whereas all the other chemicals were purchased from Aldrich and Strem and used without further purification. The NMR spectroscopic measurements were recorded on Bruker AC 200 and Bruker AVANCE 400 spectrometers. The chemical shifts are given in ppm and are relative to trimethylsilane (TMS) for ^1H and $^{13}C\{^1H\}$, to $CFCl_3$ for $^{19}F\{^1H\}$, and to 85% H_3PO_4 for $^{31}P\{^1H\}$. Elemental analyses (CHN) were carried out with a Carlo Erba 1106 elemental analyzer. The GC analyses were performed with a Varian GP-3380 gas chromatograph equipped with a Megadex-ETTBDMS-β chiral column.

NMR spectroscopic evidence of the formation of [Ru(O*i*Pr)(CNN)(dppb)] (4): Acetone (1.4 μL, 0.019 mmol) was added to a suspension of [Ru(H)(CNN)(dppb)] (**2**; 15 mg, 0.021 mmol) in C_6D_6 giving a red solution. ^1H NMR (200.1 MHz, C_6D_6, 20 °C): $\delta = 8.38$ (m, 2H; aromatic protons), 8.07 (t, $J(H,H) = 7.7$ Hz, 2H; aromatic protons), 7.90 (s, 1H; aromatic proton), 7.40–6.58 (m, 15H; aromatic protons), 6.50 (t, $J(H,H) = 7.5$ Hz, 2H; aromatic protons), 6.06 (m, 4H; aromatic protons), 4.32 (br s, 1H; NH_2), 3.69 (hept, $J(H,H) = 6.1$ Hz, 1H; OCH), 3.44 (d, $J(H,H) = 15.1$ Hz, 1H; NCH_2), 3.15 (br d, $J(H,H) = 15.1$ Hz, 1H; NCH_2), 2.91 (m, 2H; PCH_2), 2.34 (s, 3H; CH_3), 2.29–1.60 (m, 5H; CH_2, NH_2), 1.31 (m, 2H; CH_2), 0.99 ppm (d, $J(H,H) = 6.1$ Hz, 6H; $OCHMe_2$); $^{31}P\{^1H\}$ NMR (81.0 MHz, C_6D_6, 20 °C): $\delta = 55.5$ (d, $^2J(P,P) = 34.0$ Hz), 37.8 ppm (d, $^2J(P,P) = 34.0$ Hz).

NMR spectroscopic evidence of the formation of [Ru(O*i*Pr)(CNN)(dppb)]·*n i*PrOH (5): **Method a**: A 0.1 M solution of NaO*i*Pr (1.9 mL, 0.19 mmol) in 2-propanol was added to a suspension of [RuCl(CNN)(dppb)] (**1**; 97 mg, 0.128 mmol) in toluene (1.9 mL). The reaction mixture was stirred at 50 °C for 1 h giving a dark red solution. $^{31}P\{^1H\}$ NMR (81.0 MHz, 2-propanol/toluene/C_6D_6 = 5:5:1 v/v, 20 °C): $\delta = 54.3$, (d, $^2J(P,P) = 34.0$ Hz), 45.5 ppm (d, $^2J(P,P) = 34.0$ Hz).

Method b: A suspension of [Ru(H)(CNN)(dppb)] (**2**; 30 mg, 0.041 mmol) in C_6D_6 (0.4 mL) was treated with 2-propanol (0.1 mL, 1.31 mmol) and acetone (3.0 μL, 0.041 mmol) promptly leading to **5**. ^{1}H NMR (400.1 MHz, C_6D_6, 20 °C): δ = 8.37–6.05 (m, 26H; aromatic protons), 4.45 (s, 1H; OH of 2-propanol), 3.90 (hept, J(H,H) = 6.4 Hz; CH of 2-propanol), 3.87 (d, J(H,H) = 15.0 Hz, 1H; NCH_2), 3.52 (br m, 1H; NH_2), 3.30 (pseudo t, J(H,H) = 15.0 Hz, 1H; NCH_2), 2.95 (t, J(H,H) = 16.5 Hz, 1H; PCH_2), 2.74 (m, 1H; PCH_2), 2.25 (s, 3H; CH_3), 2.18 (m, 1H; PCH_2), 2.02 (t, J(H,H) = 16.5 Hz, 1H; PCH_2), 1.75 (br m, 1H; NH_2), 1.70–1.52 (m, 4H; CH_2), 1.10 ppm (d, J(H,H) = 6.4 Hz; CH_3 of 2-propanol); ^{13}C{^{1}H} NMR (100.6 MHz, C_6D_6, 20 °C): δ = 164.0–114.5 (m; aromatic carbons), 63.8 (s; OCH of 2-propanol), 52.8 (s; CH_2N), 32.1 (d; PCH_2), 30.3 (d; PCH_2), 26.8 (s; CH_2CH_2), 25.7 (s; CH_3 of 2-propanol), 22.3 (s; CH_2CH_2), 21.9 ppm (s; CH_3); ^{31}P{^{1}H} NMR (81.0 MHz, C_6D_6, 20 °C): δ = 54.2 (d, ^2J(P,P) = 34.0 Hz), 44.7 ppm (d, ^2J(P,P) = 34.0 Hz).

[Ru(CNN)(dppb)(*i*PrOH)](BAr$^f_4$) (6): Na[BAr$^f_4$] (241 mg, 0.272 mmol) was added to [RuCl(dppb)(CNN)] (**1**; 207 mg, 0.272 mmol) in dichloromethane (5 mL). The reaction mixture was stirred for 2 h at room temperature, filtered to remove NaCl, and the solvent was evaporated. The oily product was suspended in heptane (10 mL), filtered, and dried under reduced pressure. The resulting green product was dissolved in 2-propanol (3 mL) and the solvent was evaporated to obtain a green–yellow solid, which was dried under reduced pressure (334 mg, 75% yield). ^{1}H NMR (200.1 MHz, C_6D_6, 20 °C): δ = 8.37 (m, 8H; aromatic protons), 7.63 (m, 4H; aromatic protons), 7.30–6.00 (m, 25H; aromatic protons), 5.90 (d, J(H,H) = 7.3 Hz, 1H; aromatic proton), 3.46 (m, 1H; OCH), 3.09 (t, J(H,H) = 4.8 Hz, 1H; CH_2NH_2), 2.64 (m, 2H; CH_2NH_2), 2.24 (s, 3H; CH_3), 1.89 (m, 3H; CH_2 and NH_2), 1.60–1.01 (m, 6H; CH_2), 0.79 (d, J(H,H) = 6.1 Hz, 6H; CH_3), 0.65 ppm (d, J(H,H) = 4.6 Hz, 1H; OH); ^{13}C{^{1}H} NMR (50.3 MHz, C_6D_6, 20 °C): δ = 163.7 (s; NCC), 162.7 (q, J(C,B) = 49.4 Hz; CB), 157.2 (s; NCCH$_2$), 149.6–116.6 (m; aromatic carbons), 125.2 (q, J(C,F) = 272.2 Hz; CF_3), 64.9 (s; OCH), 51.8 (s; CH_2N), 31.0 (d, J(C,P) = 31.1 Hz; PCH_2), 30.4 (d, J(C,P) = 21.7 Hz; PCH_2), 27.3 (s; CH_2), 25.0 (s; $CHCH_3$), 23.3 (s; CH_2), 21.7 ppm (s; CH_3); ^{31}P{^{1}H} NMR (81.0 MHz, C_6D_6, 20 °C): δ = 54.5 (br s), 44.5 ppm (br s); ^{31}P{^{1}H} NMR (81.0 MHz, 2-propanol with C_6D_6 (10% in volume), 20 °C): δ = 58.3 (br s), 42.3 ppm (d, ^2J(P,P) = 31.5 Hz); elemental analysis (%) for $C_{76}H_{61}BF_{24}N_2OP_2Ru$: C 55.39, H 3.73, N 1.70; found: C 54.93, H 3.53, N 1.64.

Synthesis of [Ru{OCH(4-C$_6$H$_4$F)$_2$}(CNN)(dppb)] (7): Method a: A 0.1 M solution of NaO*i*Pr (3.8 mL, 0.38 mmol) in 2-propanol was added to a suspension of [RuCl(CNN)(dppb)] (**1**; 193 mg, 0.254 mmol) in toluene (3.8 mL). The reaction mixture was stirred at 60 °C for 1 h. The resulting dark-red solution was kept at room temperature for 2 h and at −20 °C for 4 h, thus affording the precipitation of NaCl, and then filtered over Celite. 4,4′-Difluorobenzophenone (67 mg, 0.307 mmol) was added to the reaction mixture, which was then stirred at room temperature for 30 min. Toluene (5 mL) was added after evaporation of the reaction mixture, and the resulting solution was kept at −20 °C for 2 h and filtered over Celite. The filtrate was concentrated (1 mL), and the addition of pentane (10 mL) afforded the precipitation of a red–orange product, which was filtered and dried under reduced pressure (216 mg, 90% yield). ^{1}H NMR (200.1 MHz, C_6D_6, 20 °C): δ = 8.12–6.37 (m, 31H; aromatic protons), 5.95 (t, J(H,H) = 7.9 Hz, 2H; aromatic protons), 5.52 (d, J(H,H) = 7.4 Hz, 1H; aromatic proton), 5.05 (br s, 1H; NH_2), 4.77 (d, J(H,P) = 3.1 Hz, 1H; OCH), 3.12–2.77 (m, 5H), 2.27 (s, 3H; CH_3), 2.06–0.90 ppm (m, 6H); ^{13}C{^{1}H} NMR (50.3 MHz, C_6D_6, 20 °C): δ = 187.4 (dd, J(C,P) = 14.6, 7.3 Hz; CRu), 163.8 (s; NCC), 161.3 (d, J(C,F) = 240.8 Hz; CF), 160.9 (d, J(C,F) = 240.5 Hz; CF), 157.2 (s; NCCH$_2$), 151.3–114.1 (m; aromatic carbons), 78.7 (s; OCH), 51.9 (d, J(C,P) = 2.7 Hz; CH_2N), 31.6 (d, J(C,P) = 28.7 Hz; CH_2P), 31.1 (d, J(C,P) = 25.6 Hz; CH_2P), 26.8 (s; CH_2CH_2), 22.5 (s; CH_2CH_2), 21.9 ppm (s, CH_3); ^{31}P{^{1}H} NMR (81.0 MHz, C_6D_6, 20 °C): δ = 57.1 (d, ^2J(P,P) = 34.3 Hz), 38.1 ppm (d, ^2J(P,P) = 34.3 Hz); ^{19}F{^{1}H} NMR (188.3 MHz, C_6D_6, 20 °C): δ = −119.5, −120.0 ppm; elemental analysis (%) calcd for $C_{54}H_{50}F_2N_2OP_2Ru$: C 68.71, H 5.34, N 2.97; found: C 68.93, H 5.41, N 2.88.

Method b: 4,4′-Difluorobenzofenone (43 mg, 0.197 mmol) was added to a suspension of [Ru(H)(CNN)(dppb)] (**2**; 135 mg, 0.186 mmol) in toluene (2 mL). The reaction mixture was stirred for 15 min, and the red solution was concentrated. The addition of pentane afforded a red precipitate, which was filtered and dried under reduced pressure (158 mg, 90% yield).

Method c: Complex **7** was prepared following the procedure described in method a with 4,4′-difluorobenzhydrol (68 mg, 0.307 mmol) in place of 4,4′-difluorobenzophenone (203 mg, 85% yield).

Synthesis of [RuCl(CNN){(*S*,*S*)-Skewphos}] (8): [$RuCl_2(PPh_3)_3$] (382 mg, 0.398 mmol) was suspended in toluene (5 mL) and (2*S*,4*S*)-bis(diphenylphosphyno)pentane ((*S*,*S*)-Skewphos; 195 mg, 0.443 mmol) was added. The reaction mixture was stirred at 110 °C for 2 h, thus giving a green solution. The solvent was removed and the residue was dissolved in 2-propanol (5 mL). 6-(4-Methylphenyl)-2-pyridylmethylamine (87 mg, 0.439 mmol) and triethylamine (0.62 μL, 4.45 mmol) were added to the reaction mixture, which was heated to reflux for 2 h. The solvent was evaporated, and the product was extracted with diethyl ether (3 × 20 mL). The resulting solution was concentrated to 10 mL and the addition of heptane afforded a yellow precipitate, which was filtered and dried under reduced pressure (231 mg, 75% yield). ^{1}H NMR (200.1 MHz, C_6D_6, 20 °C): δ = 8.26 (s, 1H; aromatic proton), 8.08 (m, 2H; aromatic protons), 7.50–6.76 (m, 18H; aromatic protons), 6.56 (m, 2H; aromatic protons), 6.25 (m, 2H; aromatic protons), 6.00 (d, J(H,H) = 6.9 Hz, 1H; aromatic proton), 3.92 (m, 1H; NH_2), 3.11 (m, 2H; CH_2N, PCH), 2.77 (m, 2H; CH_2N, PCH), 2.46 (s, 3H; CH_3), 2.19 (m, 1H; $CHCH_2$), 1.31 (dd, J(H,H), J(H,P) = 12.0, 7.4 Hz, 3H; CH_3), 1.20 (m, 1H; $CHCH_2$), 1.03 (m, 1H; NH_2), 0.53 ppm (dd, J(H,H), J(H,P) = 11.2, 6.9 Hz, 3H; CH_3); ^{13}C{^{1}H} NMR (50.3 MHz, CD_2Cl_2, 20 °C): δ = 182.0 (dd, J(C,P) = 14.1, 8.0 Hz; CRu), 163.8 (s; NCC), 157.1 (s; NCCH$_2$), 147.4–115.8 (m; aromatic carbons), 51.1 (d, J(C,P) = 2.1 Hz; CH_2N), 37.9 (t, J(C,P) = 6.0 Hz; $CHCH_2$), 32.8 (d, J(C,P) = 23.5 Hz; PCH), 21.6 (s; CH_3), 19.9 (dd, J(C,P) = 31.2, 5.7 Hz; PCH), 19.6 (d, J(C,P) = 6.6 Hz; CH_3), 17.8 ppm (d, J(C,P) = 2.5 Hz; CH_3); ^{31}P{^{1}H} NMR (81.0 MHz, C_6D_6, 20 °C): δ = 66.6 (d, ^2J(P,P) = 45.6 Hz), 47.8 (d, ^2J(P,P) = 45.6 Hz); elemental analysis (%) calcd for $C_{42}H_{43}ClN_2P_2Ru$: C 65.15, H 5.60, N 3.62; found: C 65.12, H 5.73, N 3.45.

NMR spectroscopic evidence of the formation of [Ru(O*i*Pr)(CNN)-{(*S*,*S*)-Skewphos}]·*n* *i*PrOH (9): 2-Propanol (15 μL, 0.20 mmol) was added to a suspension of [RuCl(CNN){(*S*,*S*)-Skewphos}] (**8**; 15 mg, 0.019 mmol) and NaO*i*Pr (1.8 mg, 0.022 mmol) in C_6D_6 (0.45 mL) giving a dark-red solution. ^{1}H NMR (200.1 MHz, C_6D_6, 20 °C): δ = 8.40 (m, 1H; aromatic proton), 8.26 (s, 1H; aromatic proton), 8.07 (d, J(H,H) = 8.2 Hz, 1H; aromatic proton), 8.00–6.70 (m, 17H; aromatic protons), 6.58 (t, J(H,H) = 6.7 Hz, 2H; aromatic protons), 6.25 (t, J(H,H) = 8.0 Hz, 2H; aromatic protons), 6.16 (d, J(H,H) = 7.2 Hz, 2H; aromatic protons), 3.73 (hept, J(H,H) = 6.3 Hz; CH of 2-propanol), 3.15–2.60 (m, 4H; CH_2N, PCH), 2.43 (s, 3H; CH_3), 2.40–1.45 (m; CH_2 and OH of 2-propanol), 1.28 (dd, J(H,H), J(H,P) = 12.3, 4.5 Hz, 3H; CH_3), 1.10 (d, J(H,H) = 6.4 Hz; CH_3 of 2-propanol), 0.57 ppm (dd, J(H,H), J(H,P) = 10.5, 7.0 Hz, 3H; CH_3); ^{13}C{^{1}H} NMR (50.3 MHz, CD_2Cl_2, 20 °C): δ = 184.9 (m; CRu), 163.5 (s; NCC), 158.0 (s; NCCH$_2$), 147.9–115.6 (m; aromatic carbons), 63.6 (s; CH of 2-propanol), 51.3 (d, J(C,P) = 1.8 Hz; CH_2N), 38.0 (t, J(C,P) = 6.4 Hz; $CHCH_2$), 32.5 (d, J(C,P) = 23.2 Hz; PCH), 25.1 (s; CH_3 of 2-propanol), 21.9 (s; CH_3), 20.3 (dd, J(C,P) = 29.0, 4.8 Hz; PCH), 19.7 (d, J(C,P) = 6.4 Hz; CH_3), 17.8 ppm (d, J(C,P) = 2.5 Hz; CH_3); ^{31}P{^{1}H} NMR (81.0 MHz, C_6D_6, 20 °C): δ = 65.6 (d, ^2J(P,P) = 43.3 Hz), 50.4 ppm (d, ^2J(P,P) = 43.3 Hz).

Synthesis of [Ru{OCH(CF$_3$)(4-C$_6$H$_4$F)}(CNN){(*S*,*S*)-Skewphos}] (10/11): A 0.1 M solution of NaO*i*Pr (2.9 mL, 0.290 mmol) in 2-propanol was added to a suspension of [RuCl(CNN){(*S*,*S*)-Skewphos}] (**8**; 150.0 mg, 0.194 mmol) in toluene (2.9 mL). The reaction mixture was stirred for 1 h at room temperature and the resulting dark red solution was kept at −20 °C overnight to afford the precipitation of NaCl. After filtration over Celite, CF_3CO(4-C_6H_4F) (33 μL, 0.235 mmol) was added and the solution was stirred for 1 h. The mixture of toluene/2-propanol was evaporated and then toluene (2 × 5 mL) was added and removed under low pressure to eliminate 2-propanol. The resulting product was dissolved in toluene (5 mL), the solution was kept at −20 °C for 2 h and filtered over Celite. After concentration (about 0.5 mL), the addition of pentane afforded a

red precipitate, which was filtered and dried under reduced pressure (133 mg, 74% yield). ^{1}H NMR (200.1 MHz, C_6D_6, 20°C): δ = 8.35–5.95 (m, 29H; aromatic protons), 5.64 (d, J(H,H) = 7.2 Hz, 1H; aromatic proton), 4.17 (qd, J(H,F), J(H,P) = 7.4, 3.2 Hz, 1H; CHO, major complex), 4.10 (m, 1H; NH_2), 3.89 (m; CHO, minor complex), 3.03 (m, 1H; CH_2NH$_2$), 2.63 (m, 3H; CHCH$_3$ + CH_2NH$_2$), 2.45 (s, 3H; CH$_3$, major complex), 2.41 (s; CH$_3$, minor complex), 2.06 (m, 1H; CH$_2$), 1.31 (dd, J(H,H), J(H,P) = 12.3, 7.5 Hz, 3H; CHCH_3, major complex), 1.20 (m, 1H; CH$_2$), 1.09 (dd, J(H,H), J(H,P) = 12.3, 7.3 Hz; CHCH_3, minor complex), 0.84 (m, 1H; NH$_2$), 0.48 ppm (dd, J(H,H), J(H,P) = 10.8, 7.0 Hz, 3H; CHCH_3); ^{13}C{^{1}H} NMR (50.3 MHz, C_6D_6, 20°C): δ = 185.0 (dd; J(C,P) = 13.7, 8.0 Hz; CRu), 164.2 (s; NCC), 162.0 (d, J(C,F) = 242 Hz; CF), 158.0 (s; NCCH_2), 148.6–113.6 (m; aromatic carbons and CF$_3$), 77.4 (q, J(C,F) = 27.6 Hz; CHCF$_3$), 51.2 (d, J(C,P) = 2.0 Hz; CH_2N, minor complex), 50.4 (d, J(C,P) = 2.4 Hz; CH_2N, major complex), 38.0 (m; CHCH_2), 32.7 (d, J(C,P) = 23.8 Hz; PCH), 22.1 (s; CH$_3$, major complex), 21.9 (s; CH$_3$, minor complex), 20.7 (dd, J(C,P) = 28.5, 4.1 Hz; PCH), 19.6 (d, J(C,P) = 6.6 Hz; CHCH_3), 18.0 (d, J(C,P) = 2.9 Hz; CHCH_3, major product), 17.7 ppm (d, J(C,P) = 2.7 Hz; CHCH_3, minor product); ^{31}P{^{1}H} NMR (81.0 MHz, C_6D_6, 20°C): δ = 67.0 (d, ^2J(P,P) = 44.6 Hz, minor complex), 66.7 (d, ^2J(P,P) = 44.7 Hz, major complex), 45.0 (d, ^2J(P,P) = 44.7 Hz, major complex), 44.7 ppm (d, ^2J(P,P) = 44.6 Hz, minor complex); ^{19}F{^{1}H} NMR (188.3 MHz, C_6D_2, 20°C): δ = −76.3 (s; CF$_3$, major complex), −77.0 (s; CF$_3$, minor complex), −117.5 (s; CF, major complex), −117.7 ppm (s; CF, minor complex); elemental analysis (%) for $C_{50}H_{48}F_4N_2OP_2Ru$: C 64.44, H 5.19, N 3.01; found: C 64.68, H 5.40, N 2.98.

NMR spectroscopic exchange experiments involving 2, 4, and 5: 2D ^{31}P NOESY[29] spectra were acquired in C_6D_6 or C_6D_6/2-propanol mixtures at 81.01 MHz on a Bruker AC 200 spectrometer. The data were collected at 298 K over sweep widths of 4800 Hz in both dimensions, a F2 time domain of 512 points, and 256 increments in the indirect dimension with 64 scans per increment. Quadrature detection in F1 was obtained by TPPI.[30] A relaxation delay of D1 = 0.9 s was chosen for the experiment with a mixing time of 200 ms, whereas D1 = 1.1 s for the experiment with a mixing time of 120 ms. Processing was performed with the standard Bruker software with zero filling in both dimensions to obtain 1K × 1K matrices. An exponential multiplication apodization function with a 20-Hz line broadening was applied prior to 2D FT. The chemical shifts were referenced using the spectrometer reference frequency properly adjusted for the specific solvent using H_3PO_4. The exchange values were evaluated from the cross-peak to autopeak ratios.[31]

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