Rapid Transfer Hydrogenation of Acetophenone Using Ruthenium Catalysts Bearing Commercially Available and Readily Accessible Nitrogen and Phosphorous Donor Ligands

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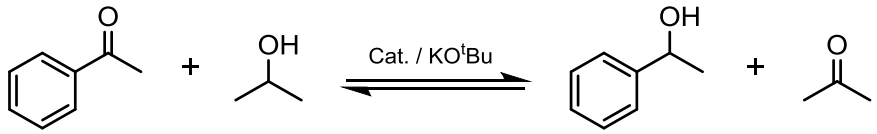
Abstract The screening, synthesis and testing of Ru complexes generated from commercially available ligands or ligands that can be synthesised in one step, is described. The catalysts were tested for activity in the transfer hydrogenation of acetophenone by isopropanol, a probe reaction for hydrogen transfer processes between oxygenated species, often found in applications such as biomass upgrading and fine and specialty chemical synthesis. Ligand screening was conducted by *in situ* catalyst generation and examined NPN and NNN pincer type ligands bearing N-H or C=N functional groups. The most active transfer hydrogenation catalysts were found to be those bearing N-H functionality, either as amino groups or as benzimidazole groups. Well-defined catalyst precursors were subsequently synthesised, including the novel complex [Ru(**1**)$PPh_3(Cl)_2$] (where (**1**) = bis(3-aminopropyl)phenylphosphine), the first reported Ru complex for this NPN ligand. Established $(PN)_2$ and PP/NN ketone hydrogenation catalysts were also screened for transfer hydrogen capability, of which [Ru($^{Ph}PN)_2Cl_2$] (where ^{Ph}PN = 2-(diphenylphosphino)ethylamine) was the most active. Subsequently, [Ru(**1**)$PPh_3(Cl)_2$], [Ru($^{Ph}PN)_2Cl_2$] and [Ru(**4**)$(PPh_3)_2Cl$][Cl] (where (**4**) = 2,6-bis(2-benzimidazolyl)pyridine) were investigated more closely to compare rate constants (determined by reaction profile regression analysis) as a more accurate measure of catalyst activity over commonly reported turn over frequencies (TOF). The effect of the reaction products on the catalyst activity was evaluated using feed spiking experiments. Catalyst deactivation was shown to be prevalent and subsequently incorporated into a simple kinetic model which enabled more accurate reaction profile fitting and provided rate constants for both the transfer hydrogenation step and deactivation reaction.

Key Words: transfer hydrogenation; ruthenium; homogeneous catalysis; pincer ligands; reaction kinetics

1. Introduction

Selective hydrogenation of carbonyl groups (C=O) is a broad field with applications across many industries, especially the fine, specialty, and renewable chemicals industries. Transfer hydrogenation (TH) of ketones to alcohols by homogeneous Ru complexes in isopropanol is a synthetically practical and important probe reaction for such reduction processes in both academic and industrial laboratories.[1-4] Scheme 1 shows the reduction of acetophenone to 1-phenylethanol by isopropanol.



Scheme 1: Reduction of acetophenone *via* the catalysed hydrogen transfer from isopropanol.

Using isopropanol (*i*PrOH) as the reducing equivalent avoids the time consuming and waste-producing work-up procedures associated with sodium borohydride reductions, and the hazards and costs of high pressure equipment needed for hydrogenation using molecular hydrogen.[5] Consequently, transfer hydrogenation can be considered a practical, green and safe reduction method.

A variety of mechanisms for Ru-based transfer hydrogenation have been proposed that include both inner sphere and outer sphere (ligand assisted) mechanisms.[6, 7] By changing the ligand architecture, remarkable improvements to the activity of Ru based transfer hydrogenation catalysts have been made. Of particular note, some of the CNN ruthenium complexes reported by the Baratta group give TOFs on the order of millions (hr^{-1}).[8] However, construction of Baratta's ligand scaffold is a multistep synthesis[9] (as is commonly the case for highly active transfer hydrogenation complexes) and that is not always practical from an industrial perspective. Therefore the development of easily synthesised Ru complexes with very high TOF for transfer hydrogenation is still an important goal. Moreover, the greatest focus of research in transfer hydrogenation catalysis to date has been in the area of asymmetric transfer hydrogenation, while somewhat neglecting the common non-chiral analogue.

Herein we report our initial efforts to develop Ru-based transfer hydrogenation catalysts of synthetic utility to the industrial research community. The present work describes the screening, synthesis and

testing of Ru complexes for the transfer hydrogenation of acetophenone using isopropanol as both reducing agent and solvent. The synthesis and characterisation of a novel NPN complex is described. To differentiate the activity of the Ru complexes better than standard initial rate approximations (TOF), a kinetic model was developed and used to calculate the reaction rate constants.

2. Experimental

2.1 General considerations

All experiments were conducted under N_2 using Schlenk line and other inert atmosphere techniques. All ligands, complexes, solid reagents and NMR solvents were stored in a N_2 filled glovebox. Acetophenone was stirred over CaH_2 overnight, distilled under reduced pressure and stored under N_2 in a foil wrapped ampoule in a refrigerator. Toluene, triethylamine and isopropanol were dried over CaH_2 overnight, distilled and subsequently stored under N_2 in an ampoule containing 4Å molecular sieves. NMR solvents were used as received. The following compounds were purchased from commercial sources and used as received and without characterisation: bis(3-aminopropyl)phenylphosphine (Alfa Aesar); 2,6-bis(2-benzimidazolyl)pyridine, $[RuCl_2(PPh_3)_3]$, acetophenone, CaH_2 (Sigma Aldrich); $[Ru(^{iPr}PN)_2Cl_2]$, $[Ru(^{Ph}PN)_2Cl_2]$ and $[Ru(^{tBu}PN)_2Cl_2]$ (Strem); 2,3-dimethyl-2,3-butanediamine dihydrochloride (TCI Europe). The following compounds were prepared according to literature procedures: N,N-bis(1H-benzimidazol-2-ylmethyl)-N-amine,[10] 2,6-bis-[1-(2-methylphenylimino)ethylpyridine,[11] and $[RuClH(PPh_3)_3$•toluene].[12]

NMR spectra were recorded using a Bruker 300 MHz spectrometer. The ^{1}H NMR and ^{13}C NMR chemical shifts were referenced to the residual protio impurity and ^{13}C signal of the deuterated solvent respectively.

Elemental analyses were carried out on an Exeter Analytical CE440 elemental analyser.

Gas chromatography (GC) analysis was conducted on an Agilent 7890A instrument equipped with an Agilent 19091J-413 column (HP-5 5% Phenyl Methyl Siloxane 300 m x 320 μm x 0.25 μm) using the following method: injection volume: 1.0 μL, He carrier gas, Split Ratio: 25:1, Flow rate: 50 mL/min, FID detector temperature: 250 °C; Temperature program: starting temperature; 50 °C (hold for 6 mins), ramp 5 °C/min to 100 °C, ramp 10 °C/min to 240 °C. Elution time: 1-phenylethanol 14.82 min, acetophenone 14.95 min.

X-ray data were recorded on an Oxford Diffraction Gemini A Ultra diffractometer at 150 K using Mo Kα radiation (λ = 0.71073 Å), and were corrected for absorption based on multiple and symmetry-equivalent reflections. The structure was solved and refined with programs of the SHELX family. Selected crystal data: $C_{30}H_{36}Cl_2N_2P_2Ru \cdot 2CH_2Cl_2$, M_r = 828.4, triclinic, space group $P\bar{1}$, a = 12.4741(3), b = 17.2350(4), c = 17.4983(4) Å, α = 86.500(2), β = 73.931(2), γ = 81.568(2)°, V = 3575.04(14) Å^3, Z = 4; 33330 reflections measured, 14936 unique (R_{int} = 0.0275), 817 refined parameters, 15 restraints to assist refinement of disordered solvent molecules, R (F, $F^2 > 2\sigma$) = 0.0367, R_w(F^2, all data) = 0.0881, goodness of fit (F^2) = 1.039, final difference map features between +0.94 and −1.38 e Å^{-3}.

2.2 Synthesis of complexes

*2.2.1 Complex [Ru(**4**)(PPh_3)$_2$Cl][Cl] (**9**)*

A Schlenk flask was loaded with [Ru(PPh_3)$_3$(Cl)$_2$] (1.2156 g, 1.268 mmol) and 2,6-bis(2-benzimidazolyl)pyridine (**4**) (0.4088 g, 1.313 mmol), to which was added 25 ml of anhydrous toluene. The mixture was stirred in an oil bath at 110 °C, for two hours, during which time a red-brown precipitate had formed. The suspension was then stirred for 16 hours at room temperature, after which time the solid was isolated *via* canula filtration and washed with 100 ml of anhydrous diethyl ether 3 times. The solid was dried under vacuum for 72 hours. Isolated mass 1.07 g, 84% yield. NMR data - ^{1}H NMR (d_4-methanol, δ): 8.53 (m, 2H), 7.60 (t, J = 8.0 Hz, 1H), 7.40 (m, 8H), 7.13 (m, 18H, PPh_3), 6.88 (t, J = 7.7 Hz, 12H, PPh_3), N*H* signals not observed due to rapid H/D exchange with CD_3OD. ^{13}C{^{1}H} NMR (d_4-methanol, δ): 152.7, 152.1, 144.1 and 135.7 (quaternary C), 134.4 (t, *o*-C of PPh_3), 133.3 (aromatic C-H), 132.4 (t, *i*-C of PPh_3),130.4 (s, *p*-C of PPh_3), 128.8 (t, *m*-C of PPh_3), 126.8, 124.5, 122.9, 122.1 and 113.6 (aromatic C-H). ^{31}P{^{1}H} NMR (d_4-methanol, δ): 22.1 (s). Elemental analysis calculated (%) for $C_{55}H_{43}Cl_2N_5P_2Ru$: C 65.54, H 4.30, N 6.95; found: C 65.40, H 4.42, N 7.03. Product is soluble in methanol, poorly soluble in ethanol, but insoluble in acetone, acetonitrile and dichloromethane. A d_4-MeOH NMR sample exposed to air was observed to form crystals after 3 hours. However, no decomposition signals were observed in the NMR spectrum. A sample of the solid exposed to air for 2 hours and returned to the glove box was analysed by NMR; new unassigned signals appeared in both the ^{1}H and ^{31}P NMR spectra.

*2.2.2 Complex [Ru(**1**)PPh_3(Cl)$_2$] (**10**)*

A Schlenk flask was loaded with [$Ru(PPh_3)_3(Cl)_2$] (2.0270 g, 2.114 mmol) and bis(3-aminopropyl)phenylphosphine (**1**) (0.4816 g, 2.147 mmol), to which was added 17 ml of anhydrous toluene to generate a yellow suspension. The mixture was stirred in an oil bath at 110 °C, for two hours. The yellow suspension was then stirred for 16 hours at room temperature, after which time the solid was isolated *via* canula filtration and washed with 100 ml of anhydrous diethyl ether 3 times. The solid was dried under vacuum for 72 hours. Isolated mass 1.20 g, 86% yield. NMR data - ^{1}H NMR ($CDCl_3$, δ): 7.71 (m with appearance of t, 6H) 7.43 (m with appearnce of t, 2H), 7.14-6.94 (m, 10H), 6.88 (m with appearance of t, 2H) 4.25, (br, 2H, N*H*), 3.39 (br, 2H, N*H* and C*H*), 3.08 (br, 1H, C*H*), 2.23-1.81 (m, 10H, 9C*H* and N*H*), 0.68 (br, 1H, C*H*). ^{13}C{^{1}H} NMR ($CDCl_3$, δ): 138.7 (d, *i*-C of PPh), 137.0 (d, *i*-C of PPh_3), 134.0 (d, *o*-C of PPh_3), 131.2 (d, *o*-C of PPh), 128.4 (s, *p*-C of PPh_3), 128.2 (s, *p*-C of PPh), 127.7 (d, *m*-C of PPh), 127.5 (d, *m*-C of PPh_3), 42.3, 40.5, 33.3 (d, $^1J_{PC}$ = 26.9 Hz), 27.9 (d, $^1J_{PC}$ = 27.8 Hz), 26.1, 25.4. ^{31}P{^{1}H} NMR ($CDCl_3$, δ): 48.8 (d, $^2J_{PP}$ = 34 Hz), 32.65 (d, $^2J_{PP}$ = 34 Hz). Elemental analysis calculated (%) for $C_{30}H_{36}Cl_2N_2P_2Ru$: C 53.93, H 5.51, N 4.25; found: C 53.72, H 5.51, N 4.52 Product is soluble in dichloromethane and chloroform, but insoluble in methanol, ethanol, isopropanol and acetonitrile. The product is air sensitive in solution, turning green on exposure to air. A sample of the solid exposed to air for 2 hours and returned to the glove box was analysed by NMR; no new unassigned signals were observed in either the ^{1}H or ^{31}P NMR spectra. Single crystals of [Ru(**1**)$PPh_3(Cl)_2$] were grown by layering hexane onto a DCM solution of the complex to enable slow diffusion of the solvents.

2.3 General procedure for transfer hydrogenation of acetophenone:

In a glovebox, a Schlenk flask was loaded with the ruthenium complex and ligand (as necessary) and an additional Schlenk flask was loaded with KO^{t}Bu. Separate stock solutions of acetophenone and KO^{t}Bu in isopropanol were prepared. The acetophenone solution was added to the flasks containing the ruthenium complexes and allowed to stir for 10 minutes before being immersed in an oil bath set to 65 ^{o}C (the temperature of the reaction solution was measured to be 56 ^{o}C, the boiling point of acetone). This reaction temperature was chosen rather than the standard 82 ^{o}C (boiling point of isopropanol) to reduce the loss of acetone which would affect the equilibrium position. After 10 minutes, the reaction was initiated by addition of the KO^{t}Bu solution. The reaction progress was monitored by taking 0.3 ml samples via syringe, aerating the sample in the syringe 3 times to prevent any further reaction, and analysing the mixture by gas chromatography. Control experiments were undertaken to confirm that aeration of the samples did quench catalytic activity.

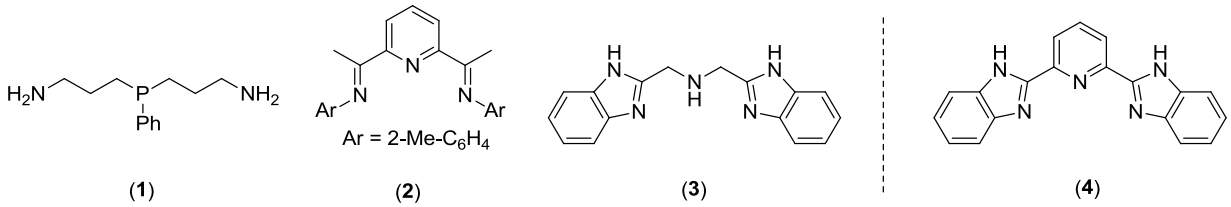
2.4 Kinetic modelling

A general kinetic model for the transfer hydrogenation of acetophenone with isopropanol was developed using Athena Visual Work Bench (Version 14.2). The model used as inputs the initial concentrations of ruthenium complex, acetophenone, isopropanol, 1-phenylethanol, and acetone. Material balances for a batch reactor where solved using the built-in differential equation solver. The built-in nonlinear parameter estimation and statistical analysis package was used initially to estimate values for rate constants of the forward reaction of a reversible transfer hydrogenation step, k_{f^1}, and the rate constant for an irreversible catalyst deactivation step, k_{f^2},. The values of k_{f^1} and k_{f^2} were subsequently used in the differential equation solver of Matlab to predict the reaction profile for each catalyst run. The concentrations of acetophenone and 1-phenylethanol were used as model responses to be compared with experimental data.

3. Results and Discussion

From the outset, we aimed to develop catalysts that utilise commercially available ligands or ones easily prepared in one step from cheap reagents. For ruthenium mediated hydrogenation and transfer hydrogenation of unsaturated hydrocarbons with C=O and C=N groups, a metal bound N-H bond within the ligand framework has proved to be a hugely successful strategy for developing effective catalysts[13] (though it should be noted that highly effective ruthenium transfer hydrogenation catalysts lacking a metal bound N-H bond have been reported such as those by Plietker[14] and Stradiotto[15]). Therefore ligands bearing N-H bonds or readily reducible imine groups were targets for this work. We identified compounds (**1**), (**2**) and (**3**), shown in Scheme 2, as potential ligands for effective transfer hydrogenation. To the best of our knowledge, these ligands have not been utilised in ruthenium mediated transfer hydrogenation chemistry. Furthermore no ruthenium complexes of ligand (**1**) have been reported. Compounds (**1**) and (**2**) are commercially available, while compound (**3**) can be easily prepared from *o*-phenylenediamine and iminodiacetic acid in one step.[10] Reports on the coordination chemistry of (**1**) are very limited[16] and it has not been reported as a ligand in catalysis. Compound (**2**) has been extensively utilised as a ligand in iron oligomerisation catalysis.[11, 17]. Benzimidazole ligands can form highly effective ruthenium hydrogenation catalysts,[18, 19] and transfer hydrogenation catalysts[20-25] therefore bis-((2-benzimidazole)methyl)-amine (**3**) was chosen for transfer hydrogenation screening. Compound (**3**) has been utilised as a ligand in butadiene oligomerisation catalysis.[10] Furthermore, there is a single report of the related compound 2,6-bis(2-benzimidazole)-pyridine (**4**), which is commercially

available, to form a ruthenium phosphine complex which is a highly efficient transfer hydrogenation catalyst.[23] Therefore compound (**4**) was included in this study for comparison purposes.



(**1**) (**2**) (**3**) (**4**)

Scheme 2. Structures of NPN and NNN precursor ligands used in this study for the preparation of Ru-based hydrogen transfer catalysts.

3.1 Transfer Hydrogenation Catalyst Screening

The potential for the compounds (**1**-**4**) to form transfer hydrogenation catalysts was explored by *in-situ* catalyst formation with $[RuCl_2(PPh_3)_3]$ for the transfer hydrogenation of acetophenone to 1-phenylethanol using isopropyl alcohol as the hydrogen donor. The reactions were benchmarked against $[RuCl_2(PPh_3)_3]$, a known transfer hydrogenation catalyst.[26-28]. However, a more recent report indicates that under TH conditions, $[RuCl_2(PPh_3)_3]$ is actually a precursor for ruthenium nanoparticles that are the active TH species.[29] Upon activation of the TH catalysts *via* the addition of KOtBu, samples were collected over time and analysed for 1-phenylethanol production.

Figure 1 shows the observed 1-phenylethanol yields from acetophenone TH at 329 K using Ru catalysts formed from ligands (**1**-**4**) and $[RuCl_2(PPh_3)_3]$ for reference. Compounds (**1**), (**3**) and (**4**) resulted in active catalysts with comparable 1-phenylethanol yields at later residence times, all of which were greater than $[RuCl_2(PPh_3)_3]$, the Ru pre-catalyst. However, significant differences in initial turn-over-frequency (TOF) (trend (**4**) > (**3**) > (**1**)) were measured. Compound (**2**) resulted in a catalyst that is less active than the Ru pre-catalyst, $[RuCl_2(PPh_3)_3]$. Additionally, as alkali bases are known to effect transfer hydrogenation in the absence of additional metals,[30, 31] a ruthenium free benchmark was also conducted in order to ascertain the contribution of KOtBu towards the observed reactivity. KOtBu was observed to contribute a low level of activity (less than 1% 1-phenylethanol yield after 2 hours) under the conditions employed (Figure S1). Therefore the contribution from the base was considered insignificant for the remainder of the studies.

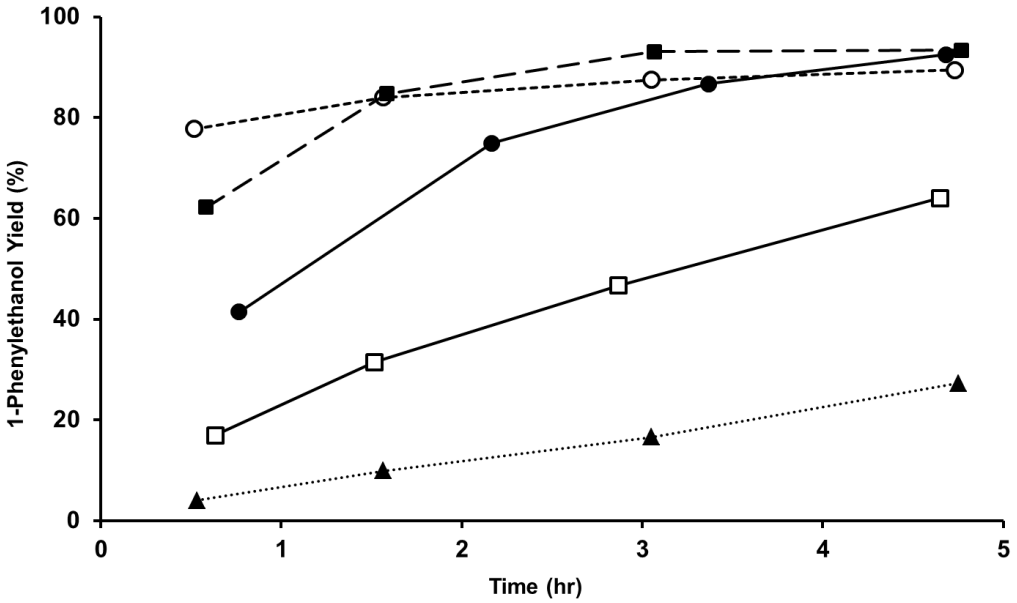
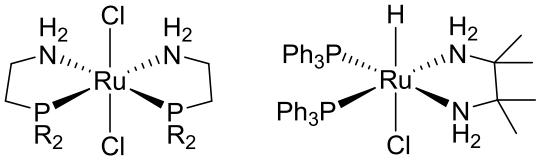


Figure 1. Reaction profiles for the transfer hydrogenation of acetophenone using Ru complexes formed *in situ* from ligands (1-4), including $[RuCl_2(PPh_3)_3]$ for reference. General conditions: [Ru complex] = 5.0 x 10^{-4} M, [KO^{t}Bu] = 1.0 x 10^{-2} M, [acetophenone] = 0.10 M; [*i*PrOH] = 12.9 M; temperature 329 K; N_2 atmosphere. Ligand (1), (●); ligand (2), (▲); ligand (3), (■); ligand (4), (○); no ligand, (□).

For comparison, additional well defined Ru complexes (Scheme 3) were tested under the same screening conditions. Complexes (**5**-**7**) are commercially available and are pre-catalysts for the hydrogenation of ketones (and imines).[32] To the best of our knowledge, complexes (**5**-**7**) have not been reported as transfer hydrogenation catalysts. Complex (**8**) has been shown to be a pre-catalyst for the hydrogenation of acetophenone, during which studies it was noted to effect "slow" transfer hydrogenation of ketones in 2-propanol, though no further details were reported in the paper.[33]



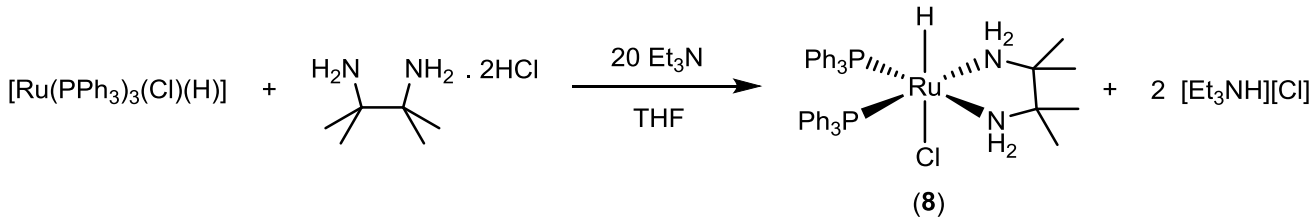
(**5**) R = Ph, (**6**) R = i-Pr, (**7**) R = t-Bu

(**8**)

Scheme 3: Structures of Ru pre-catalysts known to effect ketone and imine hydrogenation.

Complex (**8**) was synthesised by a new procedure: reacting the hydrochloride salt of the diamine $NH_2CMe_2CMe_2NH_2$ (tmen) with $[Ru(H)(Cl)(PPh_3)_3]$ in tetrahydrofuran (THF) in the presence of 20 equivalents of triethylamine (Scheme 4) (see Supplementary Information for further details). A

similar procedure has been reported in the patent literature for the synthesis of PN hydrogenation catalysts.[34]



Scheme 4: Novel procedure for the preparation of complex (**8**).

Figure 2 shows the measured yields of 1-phenylethanol from acetophenone *via* TH at 329 K using Ru pre-catalysts (**5-8**) and $[RuCl_2(PPh_3)_3]$ for reference. Complex (**5**), where R = Ph, was significantly more active for the TH of acetophenone than the other pre-catalysts evaluated. Complexes (**6**) and (**7**), where R = i-Pr and R = t-Bu respectively, showed comparable activity with (**6**) being moderately more active. Complex (**8**) resulted in a catalyst with an activity similar to $[RuCl_2(PPh_3)_3]$.

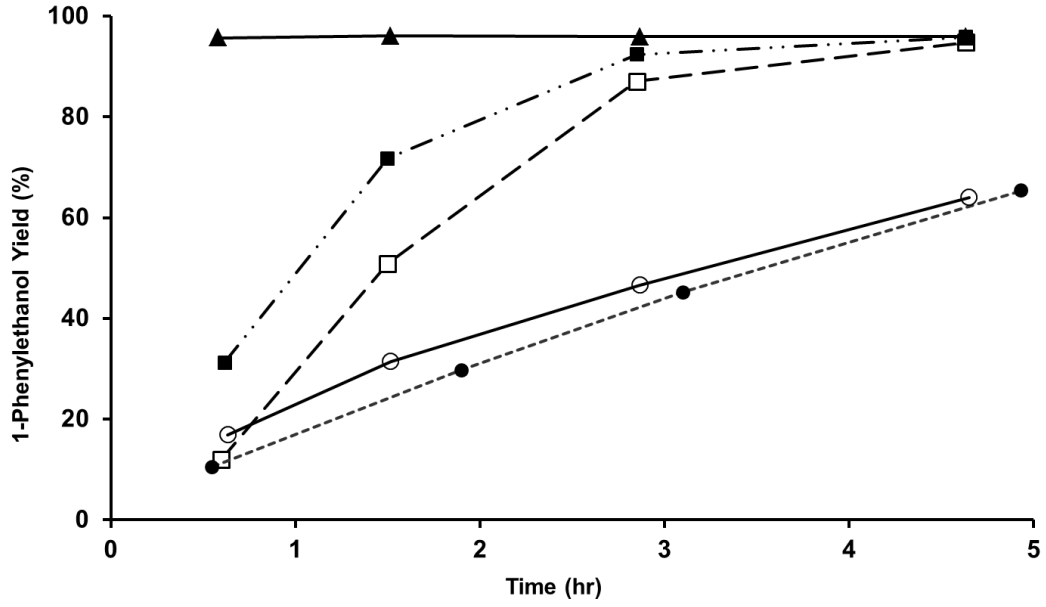
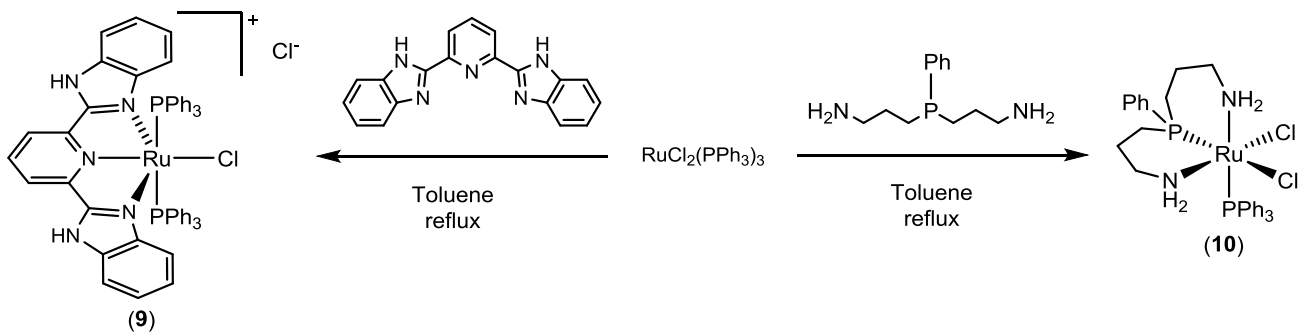


Figure 2 Reaction profiles for the transfer hydrogenation of acetophenone using Ru complexes synthesized using complexes (5-8), including $[RuCl_2(PPh_3)_3]$ for comparison.. General conditions: [Ru complex] = 5.0 x 10^{-4} M, [KO^{t}Bu] = 1.0 x 10^{-2} M, [acetophenone] = 0.10 M; [*i*PrOH] = 12.9 M; temperature 329 K; N_2 atmosphere. Complex (5), (▲); complex (6), (■); complex (7), (□); complex (8), (●); $[RuCl_2(PPh_3)_3]$, (○).

The high transfer hydrogenation activity of catalysts derived from ligands (**1**), (**3**) and (**4**) in the presence of $[RuCl_2(PPh_3)_3]$ and also from pre-catalyst (**5**) encouraged us to study these materials further for the transfer hydrogenation of acetophenone. As such, attempts to synthesise well defined complexes derived from ligands (**1**), (**3**) and (**4**) were made so comparison of their reactivity could be made with complex (**5**).

3.2 Synthesis of complexes

Complex $[Ru(\mathbf{4})(PPh_3)_2Cl][Cl]$, (**9**), and novel complex $[Ru(\mathbf{1})(PPh_3)Cl_2]$, (**10**), were successfully isolated by refluxing equimolar amounts of the ligand and $[RuCl_2(PPh_3)_3]$ in toluene, however, under analogous conditions no discernible products could be isolated from the reaction of (**2**) and $[RuCl_2(PPh_3)_3]$ (Scheme 5).



Scheme 5: Synthesis of complexes (**9**) and (**10**).

Complex $[Ru(\mathbf{4})(PPh_3)_2Cl][Cl]$, (**9**), has been previously synthesised by refluxing (**4**) with $[RuCl_2(PPh_3)_3]$ in methanol.[23, 35] However, no ^{31}P or ^{13}C NMR data have been reported. Furthermore, we have found the reported ^{1}H NMR data[36] for (**9**) to be erroneous due to ligand displacement by the NMR solvent used, $(CD_3)_2SO$ (see Supplementary Information, Figure S5). Therefore complex (**9**) and novel complex (**10**) were both characterised by elemental analyses, ^{1}H, ^{13}C and ^{31}P NMR spectroscopy. Complex (**10**) was also characterised in the solid state by X-ray crystallography. The solid state structure of complex (**9**) has been previously reported.[35]

Figure 3 shows a view of one of the crystallographically independent molecules of complex (**10**) while Table 1 gives a summary of the key crystallographic data. The asymmetric unit consists of two chemically identical but crystallographically independent ruthenium-centred complexes and four molecules of dichloromethane. The tridentate ligand has a *fac* arrangement in the distorted

octahedral Ru coordination. The two chloro ligands are mutually *cis*, and the triphenylphosphine ligand lies *trans* to one N atom and *cis* to the other donor atoms (N and P) of the tridentate ligand.

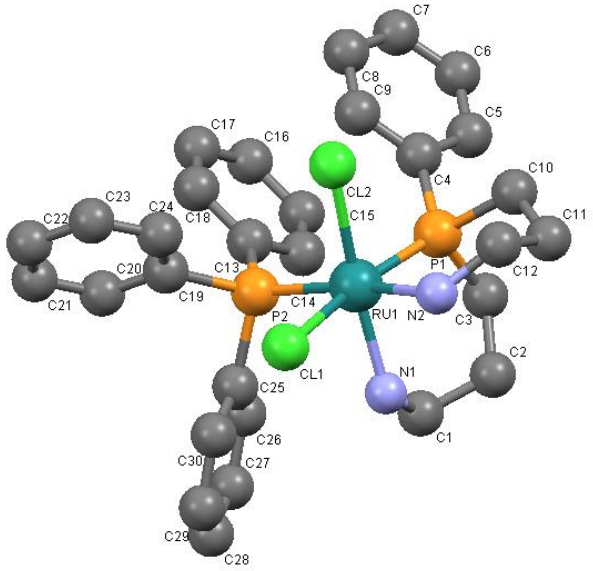


Figure 3. A view of one of the crystallographically independent complex molecules of [Ru(1)(PPh_3)Cl_2], (**10**), showing the atom numbering scheme; H atoms are omitted for clarity.

Table 1 Selected bond lengths [Å] and angles [°] for [Ru(1)(PPh_3)Cl_2], (10).

	Bond length		*Bond Angle*
Ru1-N1	2.118(2)	Cl1-Ru1-Cl2	91.59(3)
Ru1-N2	2.185(3)	P1-Ru1-P2	100.85(3)
Ru1-Cl1	2.4917(7)	N1-Ru1-N2	87.07(11)
Ru1-Cl2	2.4549(7)	P1-Ru1-N2	91.16(8)
Ru1-P1	2.2399(8)	P1-Ru1-N1	93.90(7)
Ru1-P2	2.3181(8)	P2-Ru1-Cl1	89.88(3)
		Cl1-Ru1-N1	83.96(7)
		Cl1-Ru1-N2	78.06(7)

Complex (**9**) exhibits a singlet in the $^{31}P\{^{1}H\}$ NMR spectrum (Figure S8) as expected for a *trans* bis-phosphine complex. The $^{31}P\{^{1}H\}$ NMR spectrum of complex (**10**) (Figure S3) exhibits two doublets with $^{2}J_{PP}$ = 34 Hz indicative of a *cis* bis-phosphine complex. ^{1}H and $^{13}C\{1H\}$ NMR spectra for complexes (**9**) and (**10**) (Figures S2, S4, S6 and S7) match the proposed structures and will therefore not be discussed further.

3.3 Reaction Kinetics of Highly Active Transfer Hydrogenation Catalysts

The catalytic activity of new homogeneous catalysts is very often reported in the form of turnover frequency (TOF), usually with the units $mol_{prod}.mol^{-1}{}_{cat}.hr^{-1}$. This value is commonly determined from a single experimental data point derived after a set, elapsed period of time in the catalytic test. However this routine method of catalyst evaluation is not appropriate for equilibrium controlled reactions and/or highly active catalysts (see supplementary information for a fuller discussion).

To make more accurate activity evaluations of complexes (**5**), (**9**) and (**10**) using our batch reactions, additional studies were undertaken to conduct regression analysis of reaction profiles (with limited data points) to give an estimate of the reaction rate constants. Conditions similar to those employed for the screening runs described above were used, however, due to the high TOF observed during screening, reactions were run using lower catalyst concentrations relative to the substrate and aliquots of the reaction mixture were initially taken at very short time intervals. To rule out the possibility of any of the complexes being active for transfer hydrogenation in the absence of base, samples were also taken prior to the addition of KOtBu. It should be noted that the concentration of base has been observed to affect the observed rate of reaction in Ru mediated TH reactions, particularly where low ratios of base to Ru (B/Ru) are employed.[28, 37, 38] This is exemplified by Baratta's study which showed that increasing the B/Ru ratio resulted in increasing reaction rates up to B/Ru =10.[39] Additionally, in order to investigate possible inhibition effects of the products, separate reactions were run with acetone or 1-phenylethanol added to the initial reaction mixture.

Figure 4 shows experimental results for the yield of 1-phenylethanol from complexes (**9**) (Fig. 4A), (**5**) (Fig. 4B), and (**10**) (Fig. 4C) using three different initial feed mixtures – 1) no acetone or 1-phenylethanol added (△), 2) acetone added (□), or 3) 1-phenylethanol added (◇). It should be noted that Figure 4 shows the yield of 1-phenylethanol derived from acetophenone transfer hydrogenation only. From a visual inspection it can be seen that none of the reaction profiles exhibited product inhibition from either acetone or 1-phenylethanol though previous studies have reported product inhibition for other Ru-based TH systems.[40, 41] It is also noted that the maximum yield of 1-phenylethanol (derived from acetophenone) does not change not significantly by addition of either acetone or 1-phenylethanol for complexes (**9**) and (**5**), suggesting that the equilibrium position is not significantly affected by product spiking, under the conditions employed. A similar study into Rh catalysed TH of acetophenone showed limited impact on acetophenone conversion at

similarly low acetone spiking levels.[42] The effect of base concentration on reaction rate has not been studied here however, prior to the addition of base no product was detected in any of the experiments, showing base to be essential to form catalytically active species from complexes (**5**), (**9**) and (**10**). Further we should highlight that no induction period was observed in any of the experiments conducted. As such catalyst generation was considered instantaneous upon addition of base and therefore the concentration of base was not considered in the kinetic modelling.

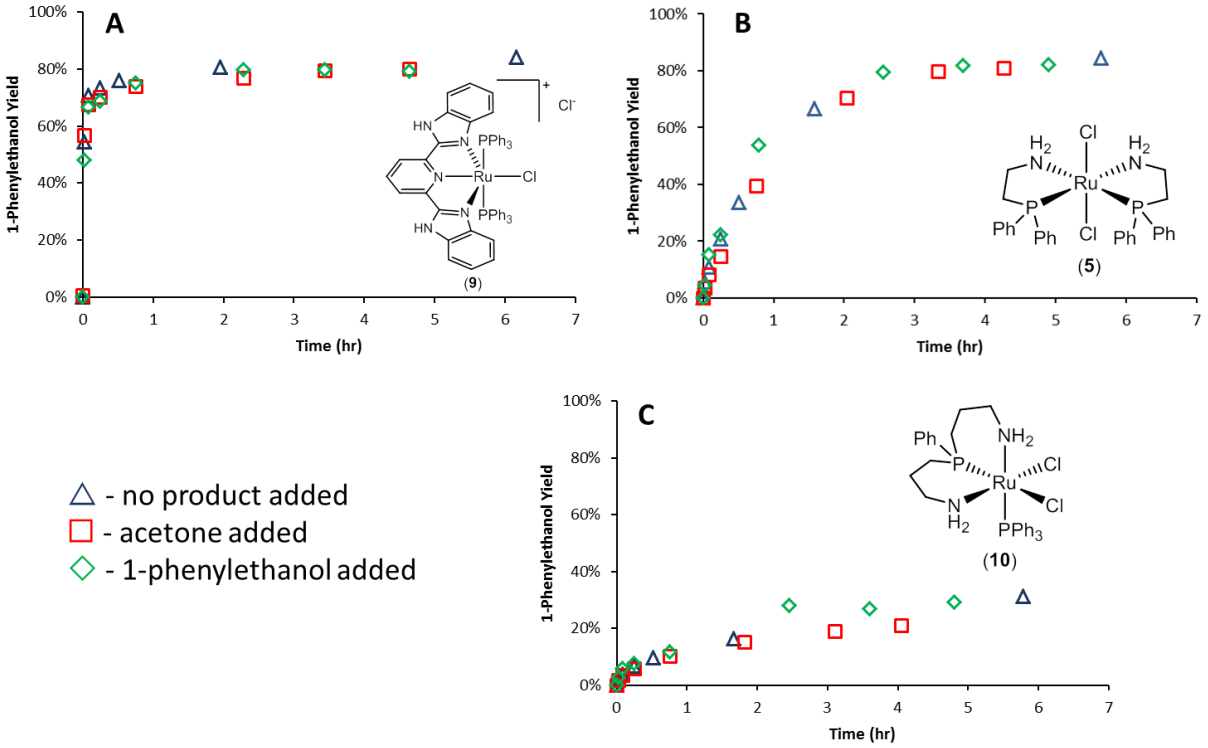


Figure 4 Reaction profiles for the yield of 1-phenylethanol resulting from the transfer hydrogenation of acetophenone at 329 K in a nitrogen atmosphere using complex (**9**) (Figure 4A); complex (**5**) (Figure 4B); and complex (**10**) (Figure 4C). Initial concentrations: [Ru complex] = 4.6 x 10^{-4} M, [KO^{t}Bu] = 1.0 x 10^{-2} M, [acetophenone] = 1.1 M, [*i*PrOH] = 11.3M, [acetone] = [1-phenylethanol] = 0 (△). Product inhibition experiments: additional to initial concentrations [acetone] = 0.2 M (□); [1-phenylethanol] = 0.2 M (◇).

Rate expressions describing the production rate of 1-phenylethanol *via* the transfer hydrogenation of acetophenone (eq. 1) in the absence of reactant and product inhibition typically have the form shown in eq. 2, where k_f is the forward rate constant, k_r is the reverse rate constant, and $[X]$ is the concentration of species X in solution.

Acetophenone + Isopropanol $\rightleftharpoons$ 1-Phenylethanol + Acetone (1)

$$R_{1-PhEtOH} = k_f[Acetophenone][IPA] - k_r[Phenylethanol][Acetone] \quad (2)$$

The equilibrium constant for the reaction is defined by eq. 3.

$$K_{eq} = \frac{k_f}{k_r} = \frac{[Phenylethanol]_{eq}[Acetone]_{eq}}{[Acetophenone]_{eq}[IPA]_{eq}} \quad (3)$$

In order to determine intrinsic rate constants, the experimental data was fitted to eq. 2 in Athena Visual Work Bench (Version 14.2) to derive values of k_f (forward rate constant) and k_r (reverse rate constant). The values of k_f and k_r were subsequently used in the differential equation solver of Matlab to predict the reaction profile for each catalyst run. However, the predicted reaction profiles were not able to satisfactorily replicate the experimental data. It was also noted that the catalyst formed from complex (**10**) does not achieve high yields of 1-phenylethanol over the reaction time tested and appears to have a decreasing catalyst activity compared to the initial rate. An additional experiment utilising complex (**9**) at very low loading (complex:substrate:solvent = 1:10,000:1,300,000) showed that equilibrium conversion was not obtained despite very high initial reaction rates (Fig. S11). These observations indicated to us that catalyst deactivation is significant and should be accounted for in the kinetic model. Accordingly, parallel processes were modelled; a reversible transfer hydrogenation reaction with a concurrent irreversible deactivation reaction. To reduce the number of parameters to be determined through the regression analysis eq. 4 was used instead of eq. 2, and the value of equilibrium the constant, K_{eq^1}, derived as 0.48 from this work (under the given reaction conditions from eq. 3). Accordingly, expressions for the formation of 1-phenylethanol ($R_{1-PhEtOH}$) and catalyst deactivation ($R_{deact.}$) are given in eq. 4 and eq. 5, respectively. A deactivation step which is second order in catalyst concentration was found to provide the best fit for the experimental data (Fig. S12).

$$R_{1-PhEtOH} = k_{f^1}[Ru]\frac{[Acetophenone][IPA]-1}{K_{eq^1}[1-Phenylethanol][Acetone]} \quad (4)$$

$$R_{deact.} = k_{f^2}[Ru]^2 \quad (5)$$

The experimental data was fitted to eq. 4 and eq. 5 in Athena Visual Work Bench (Version 14.2) to derive values of k_{f^1} and k_{f^2} which were subsequently used in the differential equation solver of Matlab to predict reaction profiles. The experimental data and predicted reaction profiles for complexes (**5**), (**9**) and (**10**) are shown in Fig. 5. Calculated values of k_{f^1} and k_{f^2} are given in Table 2. Given that product inhibition is not apparent from the reaction profiles shown in Figure 4 and the

large values of error for kinetic constants in Table 2, values of k_{f^1} and k_{f^2} were not determined for the inhibition experiments.

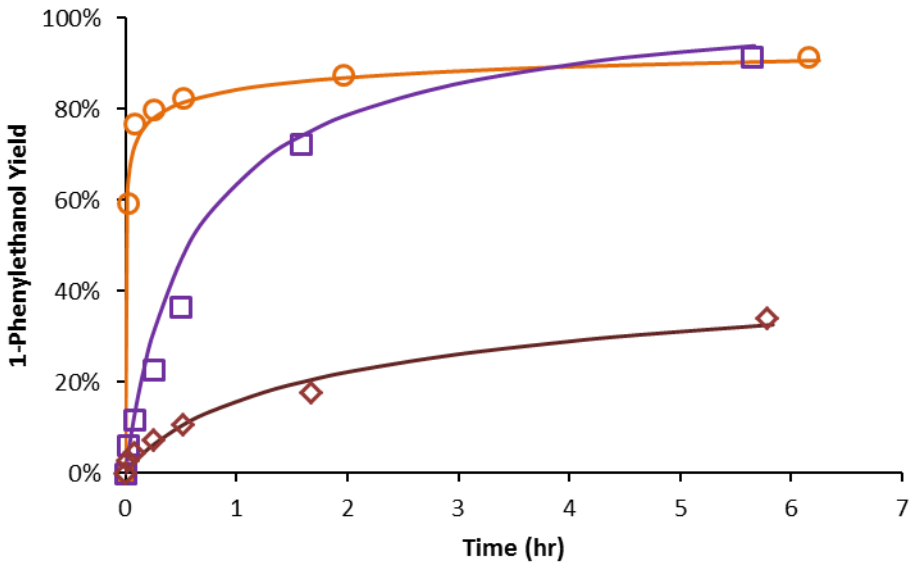


Figure 5 Experimental data for the yield of 1-phenylethanol resulting from the transfer hydrogenation of acetophenone at 329 K in a nitrogen atmosphere using complex (**9**) (○); complex (**5**) (□); and complex (**10**) (◇). Predicted reaction profiles are given as solid lines. Initial concentrations: [Ru complex] = 4.6 x 10^{-4} M, [KO^{t}Bu] = 1.0 x 10^{-2} M, [acetophenone] = 1.1 M, [*i*PrOH] = 11.3M, [acetone] = [1-phenylethanol] = 0 (△).

Table 2 Transfer hydrogenation kinetic coefficients estimated from kinetic model and model-determined equilibrium constants for experiments with no product addition (benchmark)

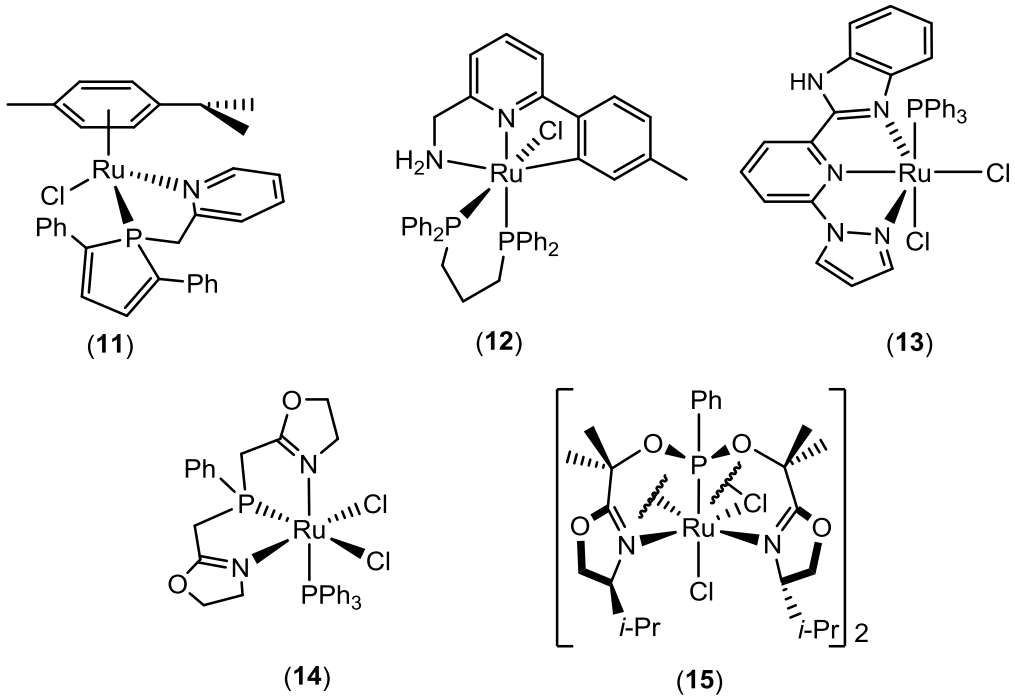
Complex (**10**)			
k_{f^1}	0.93	+/-	0.28
k_{f^2}	37	+/-	19
k_{f^2}/k_{f^1}	40		
Complex (**5**)			
k_{f^1}	5.1	+/-	1.5
k_{f^2}	36	+/-	22
k_{f^2}/k_{f^1}	7.0		
Complex (**9**)			
k_{f^1}	4200	+/-	2300
k_{f^2}	140,000	+/-	90,000
k_{f^2}/k_{f^1}	33		

As can be seen in Figure 4, for equimolar amounts of catalyst precursor used, complex (**9**) resulted in the most active catalyst followed by complex (**5**), with complex (**10**) the least active catalyst.

Examination of the calculated rate constants in Table 2 reveals that the observed trends in catalyst activity from Figure 4 are captured by the simple kinetic model. The value of k_{f1} for the catalyst generated from complex (**9**) is nearly one thousand times greater than the catalyst generated from complex (**5**) and over four thousand times greater than the catalyst generated from complex (**10**). Interestingly the deactivation rate constant, k_{f2}, is determined to be larger than the rate constant of the forward TH reaction, k_{f1}. Furthermore k_{f2}/k_{f1} indicates that the complex (**5**) is relatively more resistant to deactivation than either complex (**9**) or (**10**).

3.5 Comparison to other ruthenium TH systems

As mentioned above, remarkable improvements to the activity of Ru based transfer hydrogenation catalysts have been made. Table 3 compares the results of selected TH catalysts for the TH of acetophenone together with results from this study for complexes (**5**), (**9**) and (**10**). To be able to make comparisons with other complexes, data for complexes (**5**), (**9**) and (**10**) has been evaluated as TOF values. Le Floch's phosphole/pyridine complex (**11**)[43] and Barrata's CNN based complex (**12**)[8] form two of the most active ruthenium catalysts for the transfer hydrogenation of acetophenone when activated with base (Table 3, entry 1 and 2). Both catalysts exhibit TOF greater than 1 x 10^6 hr^{-1}. Complex (**13**), bearing a pyridine/benzimidazole/triazole NNN ligand, also reportedly achieves very high TOF for the TH of acetophenone (705,600 hr^{-1}, Table 3 entry 3) though this value is derived from a sample taken 10 seconds after initiation.[21] While these values are very high, none of these ligands are commercially available and cannot be made in a single step which represents a barrier to commercial application.

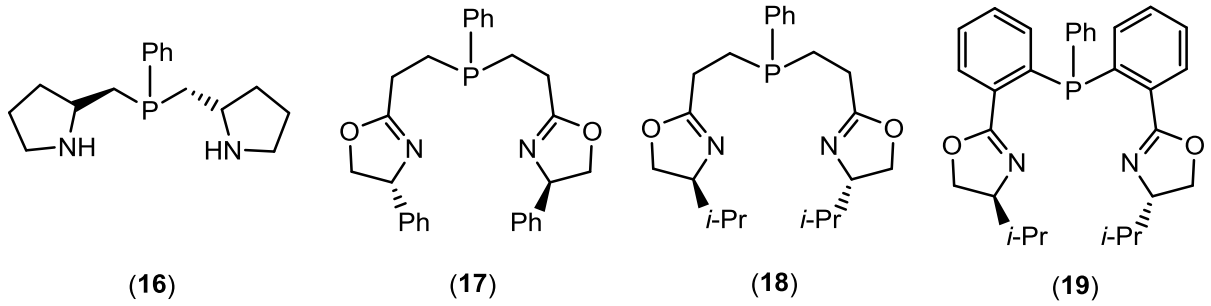


Scheme 6: Structures of well-defined ruthenium TH catalysts referred to in Table 3.

Complex (**9**), bearing the commercially available NNN ligand 2,6-bis(2-benzimidazole)-pyridine, has been shown to be a highly effective transfer hydrogenation catalyst (Table 3, entry 4). However the single literature report gives an unclear estimation for when the product sample was taken (30-40 s), leading to a TOF range of 85,500-114,000 hr^{-1}. In our hands, under similar conditions (although at a lower temperature), complex (**9**) gave a TOF of 76,500 hr^{-1}. Thus the TOF values of complex (**9**) are very similar to the best TOF value (75,000 hr^{-1}) for PP,NN ruthenium complexes bearing commercially available ligands reported by Baratta (where PP is 1,3-bis(diphenylphosphino)propane and NN is 2-aminomethylpyridine or ethylenediamine).[44] The commercially available complex (**5**) is shown here to be a competent TH catalyst which has hitherto not been reported (Table 3, entry 6).

Despite the wide application of ruthenium pincer complexes in catalysis,[45, 46] NPN ruthenium complexes for TH are remarkably scarce. To the best of our knowledge only two well defined NPN ruthenium complexes have been reported for TH catalysis, complexes (**14**)[47] and (**15**)[48] (Figure 6). Zhang has reported the use of NPN ligands (**16 - 19**) to form TH catalysts with $[RuCl_2(C_6H_6)]_2$ *in situ*, however only very modest TON and TOF were reported (Table 3, entries 10-13).[49, 50] On the other hand, complex (**14**) gave high TOF for the TH of acetophenone, 70,200 hr^{-1} after 1 min (Table 3, entry 8), while complex (**15**) gave very sluggish performance (TOF = 380 hr^{-1}, Table 3, entry 9). Braunstein reported that addition of PPh_3 to the catalytic tests run with complex (**15**) resulted in even lower TOF,[48] indicating that the poor performance of (**15**) compared to (**14**) may

be due to differences in the NPN ligands and not due to the absence of PPh_3 in the coordination sphere of the metal.



(**16**) (**17**) (**18**) (**19**)

Scheme 7: Structures of NPN ligands used to form *in situ* ruthenium TH catalysts, as referred to in Table 3.

As the novel NPN complex (**10**) reported in this work contains N-H groups,[13] we had hoped that the performance for TH of acetophenone would be comparable if not better than complex (**14**) which contains oxazoline groups. Under similar conditions (albeit lower temperature), complex (**10**) gave TOF values of 3,500 hr^{-1} (after 1 min) whereas complex (**14**) has a reported TOF value of 70,200 hr^{-1} (after 30 s). The moderate activity of (**10**) is substantially better than the TOF values reported for complex (**15**) (380 hr^{-1}, table 3, entry 9) or the *in-situ* generated catalysts reported by Zhang (less than 400 hr^{-1}, Table 3 entries 10-13). To date complex (**10**) is the first well defined NPN ruthenium complex, bearing N-H functionality, which is active for the TH of acetophenone. Therefore this report opens a new avenue for ligand design and catalyst development for the hydrogenation and transfer hydrogenation of ketones and other polar unsaturated functional groups (e.g. aldehydes, imines, and esters). While ligand (**16**) also bears N-H groups and is very similar to the NPN ligand (**1**) in complex (**10**), ligand (**16**) was screened *in-situ*, at room temperature, with low substrate loading and only sampled after 24 hours,[49] therefore the potential for NH_x-P-NH_x ligands to effect productive TH catalysis was missed.

Table 3 A comparison of selected ruthenium pre-catalysts for the TH of acetophenone.

	Catalyst	Ru:B:S	T (°C)	Time	Conv. (%)	TOF (hr^{-1})	Ref
1	(**11**)	1:10,000:20 x 10^6	90	15 hr	90	1.2 x 10^6	[43]
2	(**12**)	1:400:20,000	82	5 min	98	1.1 x 10^6 *	[8]
3	(**13**)	1:20:2,000	82	10 s	98	705,600	[21]
4	(**9**)	1:20:1,000	82	30-40s	95	85,500-114,000	[23]
5	(**9**)	1:20:2,300	56	1 min 15 min	55 74	76,500 6,860	This work
6	(**5**)	1:20:2,300	56	1 min 15 min	5.6 20.9	7,720 1,920	This work

7	(**10**)	1:20:2,300	56	1 min 15 min	2.5 6.8	3,540 642	This work
8	(**14**)	1:24:1,000	82	30 s 15 min	58.5 88	70,200 3,520	[47]
9	(**15**)	1:24:200	82	30 min 1 hr	95 98	380 196	[48]
10	(**16**) + $[RuCl_2(C_6H_6)]_2$	1:15:100	23	24 hr	96.0	4	[49]
11	(**17**) + $[RuCl_2(C_6H_6)]_2$	1:15:100	80	12 min	72	360	[50]
12	(**18**) + $[RuCl_2(C_6H_6)]_2$	1:15:100	80	1 hr	92	92	[50]
13	(**19**) + $[RuCl_2(C_6H_6)]_2$	1:15:100	80	48	94	2	[50]
* TOF calculated at 50% conversion							

While different mechanisms of TH exist for the conversion of carbonyl compounds,[6, 7] it is beyond the scope of the work here to speculate on the active mechanisms for complexes (**5**), (**9**) and (**10**). As discussed above, our experiments and data suggest that catalyst deactivation is a prevelant problem for all three catalysts, despite distinctly different ligand types. Catalyst deactivation is often not considered when determining intrinsic reaction parameters. Ligand backbone deprotonation and subsequent decomposition has been observed for some ruthenium amino phosphine complexes,[12, 51] while ligand displacement has been observed in other ruthenium TH systems,[52-54], though many other deactivation mechanisms may also be at play.[55] The exact mechanism of deactivation for complexes (**5**), (**9**) and (**10**) is not yet known. However, observation that a higher order (squared dependence) on ruthenium concentration for the rate of deactivation indicates nanoparticle formation may be operative.[29]

Work is now underway to explore further the TH, and hydrogenation, capacity of the NPN ligand framework and to determine the mechanisms of catalysis and deactivation. . Further reports on industrially relevant TH and hydrogenation catalysts will be reported in the future.

4. Conclusions

In conclusion, we have reported on the use of commercially available and readily accessible NNN and NPN pincer ligands to form ruthenium catalysts for the TH of acetophenone. *In situ* screening of ligands bis(3-aminopropyl)phenylphosphine (**1**), 2,6-bis-[1-(2-methylphenylimino)ethylpyridine (**2**), bis-((2-benzimidazole)methyl)-amine (**3**) and 2,6-bis(2-benzimidazolyl)pyridine (**4**) with $[RuCl_2(PPh_3)_2]$ afforded more active catalysts over $[RuCl_2(PPh_3)_2]$ alone when an N-H functional group was present in the ligand. Commercially available ester and ketone hydrogenation catalysts $[Ru(^{Ph}PN)_2Cl_2]$ (**5**), $[Ru(^{iPr}PN)_2Cl_2]$ (**6**) and $[Ru(^{tBu}PN)_2Cl_2]$ (**7**) were also screened for the TH of

acetophenone along with [Ru(tmen)(PPh_3)$_2$(H)(Cl)] (**8**). Surprisingly, complex (**5**) displayed substantial TH activity, which has not been reported for this complex previously. To be able to compare the activity of complex (**5**) with the most promising ligands from *in situ* screening, well defined complexes of ligands (**1**) and (**4**) were synthesised. Attempts to isolate a well-defined complex of ligand (**3**) were unsuccessful. The novel complex [Ru(**1**)(PPh_3)Cl_2], (**10**), is the first reported ruthenium complex of ligand (**1**), and while complex [Ru(**4**)(PPh_3)$_2$Cl][Cl], (**9**), has been previously reported, no ^{13}C or ^{31}P NMR data had been published. Furthermore, this work has shown the reported ^{1}H NMR data to be erroneous. To be able to compare the TH activity of catalysts (**5**), (**9**) and (**10**) more accurately than simple TOF values, TH reaction profiles were used to estimate rate constants by regression analysis (with limited data points). In the absence of base, catalysts (**5**), (**9**) and (**10**) showed no catalytic activity while reaction spiking experiments revealed no significant product inhibition (by acetone or 1-phenylethanol). Attempts to predict the reaction profiles using a simple reversible TH reaction model failed to give satisfactory results. After catalyst deactivation was found to be prevalent experimentally for complexes (**9**) and (**10**) a two step kinetic model involving reversible TH and irreversible, second order catalyst deactivation was able to fit the observed reaction profiles. Kinetic parameters derived from this model show that while complex complex (**9**) is substantially more active than for TH than complexes (**5**) or (**10**), it is complex (**5**) that is least prone to deactivation.

Acknowledgements

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Appendix A. Supplementary data

Supplementary data associated with this article can be found online.

Nomenclature

$[1 - Phenylethanol]$ = concentration of 1-phenylethanol, mol L^{-1}

$[Acetone]$ = concentration of acetone, mol L^{-1}

$[Acetophenone]$ = concentration of acetophenone, mol L^{-1}

$[Acetone]$ = concentration of isopropanol, mol L^{-1}

K_{eq^1} = overall equilibrium constant for transfer hydrogenation

k_f = forward rate constant for transfer hydrogenation, L mol^{-1} min^{-1}

k_r = reverse rate constant for transfer hydrogenation, L mol^{-1} min^{-1}

k_{f^1} = forward rate constant for transfer hydrogenation, L mol^{-1} min^{-1}

k_{f^2} = rate constant for catalyst deactivation, L mol^{-1} min^{-1}

$R_{1-PhEtOH}$ = overall rate of 1-phenylethanol production, mol L^{-1} min^{-1}

$R_{deact.}$ = rate of catalyst deactivation, mol L^{-1} min^{-1}

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