Journal Name

ARTICLE

Cooperative Interplay between a Flexible PNN-Ru(II) Complex and a $NaBH_4$ Additive in the Efficient Catalytic Hydrogenation of Esters

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Abstract: A catalyst loading of between 0.001-0.05 mol% of the PNN-bearing ruthenium(II) complex, [*fac*-PNN]RuH(PPh_3)(CO) (PNN = 8-(2-diphenylphosphinoethyl)amidotrihydroquinoline), in combination with 5 mol% of $NaBH_4$, efficiently catalyzes the hydrogenation of esters to their corresponding alcohols under mild pressures of hydrogen. Both aromatic and aliphatic esters can be converted with high values of TON or TOF achievable. Mechanistic investigations using both DFT calculations and labeling experiments highlight the cooperative role of the $NaBH_4$ in the catalysis while the catalytically active species has been established as trans-dihydride [*mer*-PN_HN]RuH_2(CO) (PN_HN = 8-(2-diphenylphosphino ethyl)aminotrihydroquinoline). The stereo-structure of the PN_HN-ruthenium species greatly affects the activity of the catalyst, indeed the cis-dihydride isomer, [*fac*-PN_HN]RuH_2(CO), is unable to catalyze the hydrogenation of esters until ligand reorganization occurs to give the trans isomer.

Introduction

The reduction of esters to alcohols can be considered as one of the most important fundamental reactions in organic chemistry and many commercial processes make use of this transformation.[1] Indeed, this reaction has attracted additional attention in recent times due to esters being identified as green fuels that can be produced by a biomass process.[2] In general, the reduction of esters requires stoichiometric amounts of metal-hydride reagents such as $LiAlH_4$, $NaBH_4$ or their derivatives.[3] However the use of such alkali metal-hydride compounds is hampered by the inherent dangers of such species, while the significant amounts of by-products generated on work-up creates further disposal issues.[4] Alternatively, the direct hydrogenation of esters to alcohols with hydrogen gas in the presence of a metal catalyst presents an elegant green sustainable method. Unfortunately, the severe operating conditions, which require temperatures of between 200 - 300 °C and pressures of around 20 - 30 megapascal (MPa), have so far restricted the wide industrial application of this approach. Nevertheless, considerable research effort has been directed to the transition metal-mediated hydrogenation of esters[5] and a significant breakthrough was made by the Milstein's group in 2006 in which a well-defined ruthenium PNN-pincer complex was found to efficiently catalyze ester hydrogenation.[6]

Subsequently, extensive investigations of other homogeneous ruthenium pincer catalysts have been developed by the groups of Milstein,[7] Saudan,[8] Kuriyama,[9] Saito,[10] Gusev,[11] Ikariya,[12] Beller[13] and others.[14] Elsewhere highly active tetradentate PNNN[15] and PNNP[16] ruthenium catalysts have been disclosed, with turnover frequencies (TOF) and turnover numbers (TON) as high as 10000 h^{-1} and 80000 respectively and, what is more, operating under much milder reactions conditions of only 80 °C and 5 MPa of hydrogen. One drawback of these systems is, however, the requirement of between 1 - 20 mol% of a strong base such as *t*-BuOK or NaOMe to facilitate activation of the catalyst. Due to the intolerance of some ester functional groups to basic conditions, such catalysts are likely to suffer problems in industrial applications leading to unwanted side reactions.

Therefore there is a considerable drive to develop new highly efficient catalytic systems than can operate either in the complete absence or in the presence of low levels of base. Herein we report the application of [*fac*-PNN]RuH(PPh_3)(CO) (PNN = 8-(2-diphenyl phosphinoethyl)amidotrihydroquinoline) (**A**, Chart 1) as a (pre-) catalyst for the hydrogenation of alkyl esters that operates efficiently under relatively mild conditions. On addition of $NaBH_4$ (5 mol%), **A** can hydrogenate a multitude of ester types incorporating

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Electronic Supplementary Information (ESI) available: Additional catalytic studies, NMR spectra for all the complexes and alcohols, an additional computational study of the methanol assisted isomerization of 1' to 1 along with an xyz file containing all optimized structures and their absolute free energies, See DOI: 10.1039/x0xx00000x

a broad range in steric and electronic properties. Moreover, we disclose a combined computational and experimental investigation

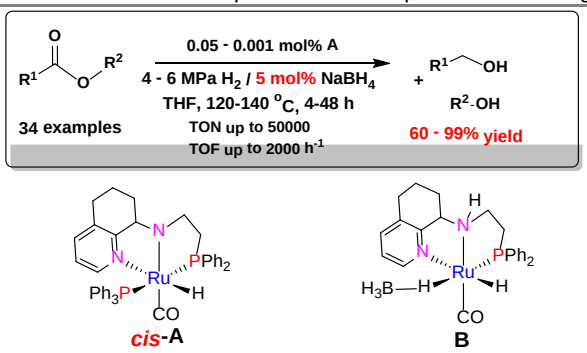


Chart 1. Efficient Catalyst A for Ester Hydrogenation

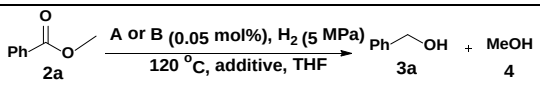
to elucidate the mechanistic details of the catalysis which has provided compelling evidence for a cooperative process involving an interplay between the PNN-ruthenium complex and the $NaBH_4$ additive.

Results and discussion

Catalytic Studies.

In previous studies, we have shown that **A** can serve as a competent catalyst for the coupling cyclizations of γ-aminoalcohols with secondary alcohols (Chart 1).[17] We now demonstrate the versatility of **A** by highlighting its capacity, in the presence of sodium borohydride, to efficiently mediate the conversion of esters to alcohols using hydrogen gas.

Table 1. Reduction of methyl benzoate (**2a**) by hydrogen in the presence of **A** or **B**[a]

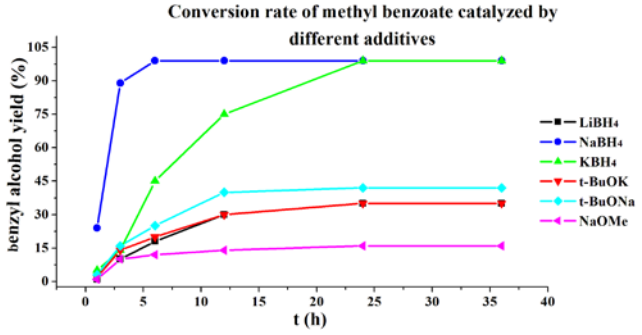


Entry	Catalyst	Additive (mol%)	Time (h)	Conv. (%)[b]
1	**A**	none	24	2
2	**A**	*t*-BuOK (10)	24	35
3[c]	**A**	*t*-BuOK (10)	36	98
4	**A**	$NaBH_4$ (5)	4	99
5	**B**	none	4/24	12/36
6	**B**	*t*-BuOK (10)	24	39
7	**B**	$NaBH_4$ (5)	3.5	99
8[d]	**C**	$NaBH_4$ (5)	24	5
9	**none**	$NaBH_4$ (5)	24	1

[a] Conditions: methyl benzoate (20 mmol), catalyst (**A** or **B**) (0.01 mmol), THF (50 mL), H_2 (5 MPa), T (120 °C). [b] The conversions were determined by GC (n-tridecane as internal standard) with respect to benzyl alcohol. [c] Methyl benzoate (10 mmol), **A** (0.02 mmol), THF (50 mL), H_2 (5 MPa), T (140 °C). [d] **C** is $RuCl(H)(CO)(PPh_3)_3$

Complex **A** was in the first instance evaluated as a catalyst for the hydrogenation of esters by using methyl benzoate (**2a**) as the test substrate (Table 1). Under the conditions of substrate/catalyst (S/C) ratio = 2000, H_2 = 5 MPa, T = 120 °C, THF as solvent and a reaction period of 24 hours, only 2% of **2a** was hydrogenated (entry 1). However, on addition of 10 mol% of *t*-BuOK to the reaction mixture, the catalytic activity of **A** increased with 35% of **2a** being reduced to benzyl alcohol (entry 2). Raising the temperature and extending the reaction duration with the same additive saw the conversion to benzyl alcohol further rise to 98% (entry 3). Significantly, however, when 5 mol% of $NaBH_4$ was added in place of *t*-BuOK, with the temperature restored to 120 °C, a surprising result was observed; the target reaction was complete after only four hours generating benzyl alcohol in almost quantitative conversion (99%) (entry 4). For purposes of comparison, $RuCl(H)(CO)(PPh_3)_3$ (the precursor to complex **A**), was additionally screened and in this case only 5% of methyl benzoate was reduced (entry 8). By contrast, in the absence of **A**, only 1% of methyl benzoate was reduced (entry 9).

Figure 1. Effect of additives in the hydrogenation of methyl benzoate (**2a**) using **A**.[a]



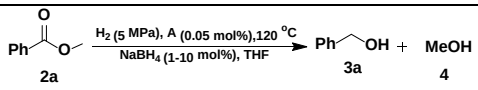
[a] Conditions: methyl benzoate (20 mmol), **A** (0.01 mmol), additive (2 mmol), THF (50 mL), H_2 (5 MPa), T (120 °C). The yield was determined by GC (n-tridecane as internal standard) with respect to benzyl alcohol.

With a view to establishing the most compatible additive for the catalytic hydrogenation of **2a** using **A**, six examples were screened namely, $LiBH_4$, $NaBH_4$, KBH_4, *t*-BuOK, *t*-BuONa and NaOMe under the same reaction conditions (Table S1 and Fig. 1). It was found that the type of additive introduced had a significant effect on the rate and yield of the ester hydrogenation with $NaBH_4$ the standout performer. When the same amount of KBH_4 was employed, the rate of hydrogenation observed over 4 hours is notably less than that seen with $NaBH_4$, with comparable high conversions to benzyl alcohol being reached after 24 and 6 hours, respectively. On the other hand, with $LiBH_4$ ($LiBH_4$ is unstable and undergoes facile decomposition) as the additive only 36% of benzyl alcohol is produced after 36 hours. Among the different additives screened, $NaBH_4$ was also found to be better than *t*-BuOK, *t*-BuONa and NaOMe (Table S1 and Fig. 1).

In order to determine the optimal quantity of $NaBH_4$ required for the hydrogenation of **2a** using **A**, six differing amounts were screened under the same reaction conditions: 1 mol% $NaBH_4$, 2.5 mol% $NaBH_4$, 5 mol% $NaBH_4$ and 10 mol% $NaBH_4$ (Table 2). It was found that use of 5% mol of $NaBH_4$ gave the best conversion over the shortest time. By contrast, use of 1 and 2.5 mol% $NaBH_4$ did not

prove sufficient for a complete ester hydrogenation reaction (entries 1, 2), while use of 10 mol% gave no beneficial

Table 2 Hydrogenation of methyl benzoate (**2a**) using different catalytic amounts of $NaBH_4$.[a]

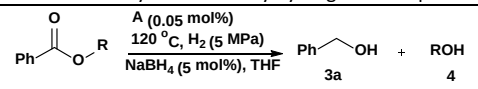


Entry	$NaBH_4$ (mol%)	H_2 (Mp)	Time (h)	Conv.(%) by GC[b]
1	1	5	12	25
2	2.5	5	12	56
3	5	5	4	99
4	10	5	1/3/3.5	24/90/99

[a] Conditions: methyl benzoate: 20 mmol, **A** (0.01 mmol), $NaBH_4$ (0.2-2 mmol), THF (50 mL), H_2 (5 MPa), T (120 °C).[b] The conversion was determined by GC respect to benzyl alcohol.

catalytic efficiency when compared to that observed with 5 mol% $NaBH_4$ (entries 3, 4). With the view to optimize the temperature of the ester hydrogenation reaction, we screened it at 80 °C, 100 °C and 120 °C. At 120 °C, the conversion reached up to 99% in 4 hours. On the other hand, at 80 °C and 100 °C, conversions of 90 and 99% were only achieved after 24 and 12 hours, respectively (see SI, Tables S2). Hence, when the temperature was lower than 120 °C, the catalytic efficiency decreased significantly. A variety of different conditions was also investigated (see SI, Tables S3-S5). Of the solvents screened, THF was a better choice than ethanol or 1,4-dioxane (see SI, Tables S3). With regard to the different hydrogen pressures screened, 5MPa of hydrogen proved more suitable than at lower pressures (0.1-3 Mp of H_2) (see SI, Tables S4). Overall, it was found that the reaction was best conducted in THF at 120 °C under 5MPa of hydrogen pressure affording benzyl alcohol in high yield (99%) after 4 hours.

Table 3. Reduction of alkyl benzoates by hydrogen in the presence of **A**.[a]



Entry	R	Time (h)	Conv.(%)[b]	TON
1	Me (**2a**)	4	99 (95 [c])	1980
2	Et	12	99 (95 [c])	1980
3	*i*-Pr	12	98 (94 [c])	1960
4	*n*-Bu	12	97 (94 [c])	1940
5	CH_2Ph	12	90 (85 [c])	1800
6	*t*-Bu	24	10 (8 [c])	200

[a] Conditions: alkyl benzoate (20 mmol), **A** (0.01 mmol), $NaBH_4$ (1 mmol), THF (50 mL), H_2 (5 MPa), T (120 ℃). THF = tetrahydrofuran.[b] The conversion was determined by GC (n-tridecane as internal standard) with respect to benzyl alcohol. [c] Yield of the isolated product

With a view to gaining a broader understanding of the catalytic performance of **A**, we screened this complex for the hydrogenation of a wide variety of esters (Tables 3 – 5). Indeed, a range of different linear and branched alkyl benzoates were reduced to their corresponding alcohols using the conditions, 0.05 mol% of **A**, 5 mol% $NaBH_4$ and under 5 MPa of hydrogen pressure at 120 °C in THF (Table 3). While the Me, Et, *i*-Pr, *n*-Bu and CH_2Ph benzoates were smoothly reduced to their corresponding benzyl alcohols with high conversions (entries 1-5), the reduction of tert-butyl benzoate only proceeded in low conversion (10%) after 24 hours (entry 6); this latter observation has been attributed to steric effects imparted by the bulky alkyl group.

To explore the tolerance of the catalyst generated from **A** and $NaBH_4$, we investigated a wide selection of methyl benzoates (**2b** – **2t**), in which the substitution pattern of the aryl group was systematically varied at the ortho-, meta- and para-positions (Table 4). Large turnover numbers were observed for methyl 3-(trifluoromethyl)benzoate (**2h**) and methyl 4-(trifluoromethyl)benzoate (**2l**) with **2l** notably achieving a TON of 56000 (S/C = 100000, 56% conversion) over 30 hours at 140 °C. In general, selective hydrogenation was observed for all the substituted benzoates except phenolic **2q**, highlighting the tolerance of **A**/$NaBH_4$ to a broad range of substituents including halide groups. Clearly, electronic and steric effects within the ester influence the reactivity. For example, the electron-rich benzoates **2o**, **2p** and **2r** gave significantly lower yields of the corresponding alcohols when compared to the relatively electron-poor **2k**, **2l**, **2m** and **2n** (Table 4). This can be credited to the electron-poor aromatic ring being able to increase the polarity of the carbonyl group in **2** and hence making it more favourable to the addition of hydride. This increased polarity is of course enhanced by the presence of very good electron withdrawing groups such as trifluoromethyl group leading to the highest turnover numbers. The benzoates containing para- and meta-substituted halides are more reactive their ortho-substituted counterparts (Table 4), which can be attributed to the steric hinderance imparted by the ortho-halogens in the aromatic ring, thus making hydride transfer to the carbonyl group of aromatic esters less favourable. However, the only ester of the series to be screened that did not to give any hydrogenated product was methyl 4-hydroxybenzoate; this is likely due to the phenolic OH in **2q** reacting either with $NaBH_4$ or with the PNN-Ru species, making **A** inactive toward ester reduction. [14(d)]

To further examine the substrate scope of **A**/$NaBH_4$, aliphatic esters were also assessed (Table 5). It was found that once again these more challenging esters could be smoothly reduced to their corresponding alcohols in high yields under the same reaction conditions. Ethyl trifluoroacetate could be hydrogenated with a TON of 6560 (entry 1), while Me, Et, *n*-Pr and *n*-Bu acetates also gave high conversions to the corresponding alcohols; the variations in TOF's are likely due to differences in electronic and steric effects (entries 2-5). The reduction of tert-butyl acetate only proceeded in a low yield (14% conversion after 24 h; entry 6), due to the presence of the bulky alkyl group. Moreover, an excellent yield and conversion were obtained for the α,β-unsaturated ester methyl cinnamate, giving 3-phenyl-1-propanol. Given these encouraging results we found that **A**/$NaBH_4$ proved capable of hydrogenating a wide selection of other esters (entries 7-9).

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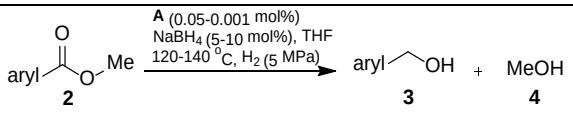
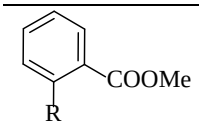
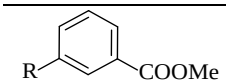
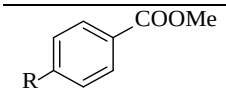
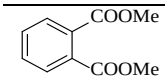
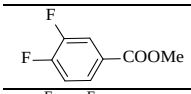
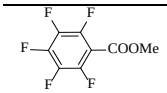
Table 4. Reduction of various methyl benzoates (**2b** – **2t**) with different aryl group substitutions by hydrogen in the presence of **A**.[a]

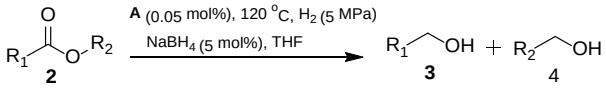


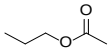
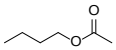
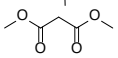
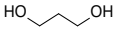
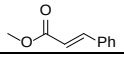
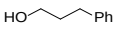
2 **3** **4**

Structure	Compound	S/C ratio	Time (h)	Conv. (%)[c]	Yield (%)[d]	TON
	**2b** (R = F)	2000	18	65	60	1300
	2c (R = CF_3)	8000	16	99	95	7920
	2c (R = CF_3)	20000	28	85	82	17000
	2d (R = Cl)	2000	12	93	85	1860
	2d (R = Cl)	8000	24	65	60	5200
	2e (R = Br)	2000	12	90	85	1800
	2e (R = Br)	8000	24	60	56	4800
	2f (R = I)	2000	12	83	76	1660
	**2g** (R = F)	2000	12	97	93	1940
	2g (R = F)	20000	24	75	72	15000
	2h (R = CF_3)	2000	5	99	94	1980
	2h (R = CF_3)	20000	18	98	92	19600
	2h (R = CF_3)	100000[b]	30	48	42	48000
	2i (R = Cl)	2000	8	95	90	1900
	2i (R = Cl)	16000	24	93	88	14880
	2j (R = Br)	2000	8	99	93	1980
	2j (R = Br)	20000	24	92	85	18400
	**2k** (R = F)	2000	12	94	91	1880
	2k (R = F)	20000	24	74	71	14800
	2l (R = CF_3)	2000	4	99	95	1980
	2l (R = CF_3)	20000	18	96	92	19200
	2l (R = CF_3)	100000[b]	30	56	51	56000
	2m (R = Cl)	2000	8	93	90	1860
	2m (R = Cl)	16000	24	91	86	14560
	2n (R = Br)	2000	8	99	94	1980
	2n (R = Br)	20000	24	90	86	18000
	2o (R = OMe)	1000	24	75	70	750
	2p (R = Me)	2000	24	59	50	590
	2q (R = OH)	2000	24	None	none	none
	**2r**	1000	24	45	30	450
	**2s**	8000	24	65	50	5200
	**2t**	8000	12	75	65	6000

[a] Conditions: substrate (20-200 mmol), **A** (0.01-0.002 mmol), $NaBH_4$ (2-10 mmol), THF (50 mL), H_2 (5 MPa), T (120 °C), S/C ratio = substrate to catalyst ratio.[b] Conditions: substrate (200 mmol), **A** (0.002 mmol), $NaBH_4$ (20 mmol), THF (50 mL), H_2 (5 MPa), T (140 °C). [c] The conversion was determined by GC analysis (n-tridecane as internal standard). [d] Yield of the isolated product.

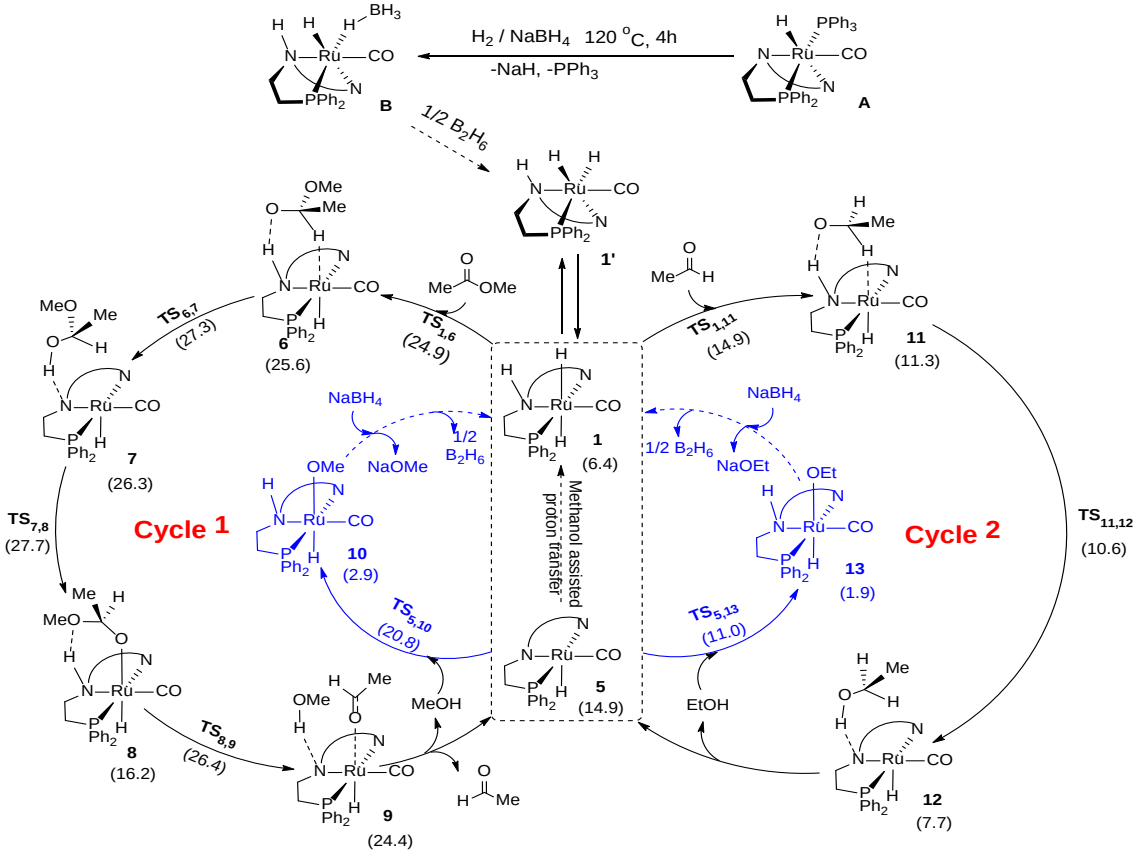
Table 5. Reduction of various aliphatic esters by hydrogen in the presence of **A**.[a]



Entry	Ester	Alcohol	Time (h)	Conv. (%)[b]	TON
1			4 24[c]	98 82	1960 6560
2			8	97	1940
3			8	96	1920
4			12	95	1900
5			18	96	1920
6			24	14	280
7			12	91	1820
8			18	95	1900
9			24	75	1500
10			18	97 (87[d])	1940

[a] Reaction conditions: substrate (20 mmol), **A** (0.01 mmol), $NaBH_4$ (1 mmol), THF (50 mL), H_2 (5 MPa), T (120 °C). THF = tetrahydrofuran.[b] The conversion was determined by GC (n-tridecane as internal standard). [c] Reaction conditions: substrate (80 mmol), **F** (0.01 mmol), S/C = 8000. [d] Yield of the isolated product.

Scheme 1. Proposed inter-linked catalytic cycles for the hydrogenation of methyl acetate to methanol and ethanol. The numbers in parenthesis are the relative free energies given in kcal/mol.



Mechanistic and Computational Investigations

To allow a detailed understanding of the role played by $NaBH_4$ in promoting the performance of **A**, we carried out DFT calculations on a series of potential steps involved in the hydrogenation of methyl acetate to give methanol and ethanol. Further computational details are provided in the SI.

It was first considered likely that complex [*fac*-PN_HN]RuH(η^1-BH_4)(CO) (**B** in Chart 1) would be formed when **A** (in Chart 1) is treated with $NaBH_4$, as related η^1-BH_4 complexes have been prepared and reported as effective catalysts for the hydrogenation of esters by Kuriyama[9a] and Beller.[13d] Indeed **B** can be isolated in reasonable yield on reaction of **A** with $NaBH_4$ in the presence of hydrogen gas, but was unexpectedly found to be an ineffective catalyst when employed in the absence of $NaBH_4$ (Table 1, entries 5-7). In agreement with the experimental result, our calculations reveal that **B** cannot hydrogenate methyl acetate directly because of a very high barrier of 44.8 kcal/mol (see SI, Scheme S1, $\mathbf{TS_{B,I}}$). Instead, the trans-dihydride complex **1** is the actual catalyst for the hydrogenation of methyl acetate. An overall mechanism for the hydrogenation of methyl acetate catalysed by **1** is shown in Scheme 1. This mechanism involves two interlinked catalytic cycles with the cooperation of BH_4^-.[6,7(a),(f),13(a),14(d),18]

At the start of Cycle 1, a methyl acetate molecule approaches **1** and directly transfers a hydride from the Ru center to its unsaturated carbonyl carbon through $\mathbf{TS_{1,6}}$. The resulting unstable intermediate **6** is 19.2 kcal/mol higher in free energy than **1**. The $(MeO)(Me)CHO^-$ group in **6** readily abstracts a proton from the N atom of the neutral PN_HN ligand through transition state $\mathbf{TS_{6,7}}$ and forms the hemiacetal intermediate **7**. **1** → **6** → **7** is representative of an outer-sphere bifunctional mechanism[6,7(a),(f),13(a),14(d)].

Subsequently, the hemiacetal **7** returns a proton to the PNN ligand, rearranges and forms **8** *via* $\mathbf{TS_{7,8}}$. The C-OMe bond in **8** is then broken through transition state $\mathbf{TS_{8,9}}$ with the formation of methanol and acetaldehyde in **9** in a manner similar to that proposed by Wang *et al*. (*i.e.* through a bifunctional double hydrogen transfer (BDHT)).[18(a)] The release of molecules of methanol and acetaldehyde affords **5**. In this case the active catalyst **1** can be regenerated from **5** through either methanol assisted H_2 activation or transfer hydrogenation with the $NaBH_4$ and alcohols. The latter pathway is more energetically competitive with a total free energy barrier of 27.7 kcal/mol. However, it does not rule out the potential involvement of a methanol assisted proton transfer step with a total free energy barrier of 30.8 kcal/mol (**1'** → $\mathbf{TS_{3,2}}$, see Fig. S4 in SI). Cycle 2 is the hydrogenation of the acetaldehyde to ethanol with a similar hydride transfer and a proton transfer. Regeneration of the active catalyst **1** (from **5**) can again occur by one of two pathways either a methanol assisted proton transfer or through hydrogen transfer with the $NaBH_4$ and alcohols. Similar to Cycle 1, the pathway is more energetically competitive but does not rule out the potential involvement of a methanol assisted proton transfer step. From the above two cycles, we can conclude that $NaBH_4$ plays a key role in the catalytic reaction by assisting the regeneration of the active catalyst.

In order to further support the cooperative interplay between **B** and $NaBH_4$ highlighted in the computational study, we additionally explored the conversion rates of methyl benzoate (20 mmol) using **B** i) in the absence of $NaBH_4$ (5 MPa H_2, T 120 °C), ii) with 0.05 equivalents of $NaBH_4$ (5 MPa H_2, T 120 °C and iii) with a stoichiometric amount of $NaBH_4$ (20 mmol) but no hydrogen (0 MPa H_2, T 120 °C). In the absence of hydrogen and in the presence of a stoichiometric amount of $NaBH_4$, **B** facilitates almost quantitative conversion of methyl benzoate in 3 hours. By contrast with 0.05 equivalents of $NaBH_4$ and 5 MPa of hydrogen, **B** achieved 92% conversion (*c.f.* 89% for **A**) over the same time period. On the other hand when methyl benzoate was hydrogenated using **B** alone with 5 MPa hydrogen, the yield was only 10% after 3 hours and 36% after 36 hours (see SI, Table S6, Fig. S1). These findings further underline the capacity of $NaBH_4$ to not only promote the conversion of **A** to **B**, but also to maintain the activity of **B** and **1** during the organic transformation. Furthermore, it has been demonstrated that $NaBH_4$ can also be the sole source of hydrogen in the ester hydrogenation. Hence these findings are fully consistent with the computed mechanism based on DFT calculations.

To understand the degree of interaction of the borohydride additive with the ester, the hydrogenation of methyl benzoate catalyzed by **A** was carried out in the presence of $NaBD_4$ (5 mol%) in THF at 120 °C. Benzyl alcohol was formed with the C-H resonances appearing at δ 7.33 (m, 5H) and δ 4.62 (s, 1.82H) in the ^{1}H NMR spectrum. The methylene signal at δ 4.62 suggests that two hydrides in the benzyl alcohol were partially substituted by deuterium (10%) (see SI, Table S7). This degree of deuteration was further corroborated by GC–MS (see SI). It implies that as expected, all of the $NaBH_4$ participates in the overall transformation and supports the role of 5 mol% $NaBH_4$ in promoting the rate of hydrogenation. In another experiment the hydrogenation of benzaldehyde catalyzed by **A**/$NaBH_4$, formed benzyl alcohol in two hours in high yield (98%), indicating that hydrogenation of benzaldehyde to benzyl alcohol is not the rate-determining step in the full transformation (see SI) and hence consistent with the computational result.

Conclusions

We have demonstrated that the PNN-bearing ruthenium(II) complex **A**, in combination with a 5 mol% loading of $NaBH_4$, is an effective catalyst for the reduction of both aromatic and aliphatic esters under relatively mild conditions. The catalytic activity for the hydrogenation of substituted benzoates esters was greatly affected by electronic, conjugative and steric effects. Electron withdrawing groups on the aromatic ring increase the reactivity while electron-donating groups decrease it. For the tert-butyl esters, the reactivity towards hydrogenation is low due to steric effects. For 4-trifluoromethyl benzoate, a very high TON of 56000 (S/C = 100000, 56% yield) is achieved in 30 hours at 140 °C using **A**. The mechanism for the hydrogenation of methyl acetate has been investigated in detail using a combined computational (DFT) and experimental approach and has revealed that trans-dihydride **1** is the active catalyst and is formed by a series of steps: **A**→**B** (isolated)→**1'**→**1**. Furthermore two linked catalytic cycles are operational that account for the formation of methanol and ethanol with the rate-determining step being most likely the cleavage of the O-H bond in

(MeO)(Me)CHOH. Most significantly, it has been confirmed by isotopic labelling and DFT calculations that $NaBH_4$ participates cooperatively with the PNN-Ru complex in both catalytic cycles and it is this feature that we attribute to the high catalytic values for the TON or TOF. This cooperative catalysis presents a promising solution for the hydrogenation of esters and carboxylic acid derivatives in a future industrial process.

Experimental section

General information.

Unless otherwise stated, all manipulations were performed under an atmosphere of argon or using standard Schlenk techniques. Solvents were dried using standard procedures and degassed with nitrogen. NMR spectra were recorded on a Bruker Avance-III (500 MHz) spectrometer. All ^{31}P chemical shifts are relative to 85% H_3PO_4. ^{1}H and ^{13}C chemical shifts were measured relative to the solvent peaks but they are reported relative to TMS. Chemical shifts were reported upfield to TMS (0.00 ppm) for ^{1}H NMR spectra and relative to $CDCl_3$ (77.0 ppm) for ^{13}C NMR spectra. Column chromatography was performed using silica gel (200-300 mesh). GC analysis was carried out on Angilent 6820 Series instrument using a capillary column (part number 19091N-113 HP-INNOWAX). GC-MS analysis was carried out on a Bruker SCION TQ GC-MS/MS.

Catalytic study details.

Under an atmosphere of argon, a stainless steel 100 mL autoclave, equipped with a magnetic stir bar, was charged with **A** (0.4 - 0.005 mmol), the desired amount of base (*t*-BuOK, *t*-BuONa, NaOMe or $NaBH_4$) (1.0 - 2.0 mmol) and the solvent to be used (50 - 75 mL). Then a solution of the ester (20 - 100 mmol) in the solvent (4 mL) was added via syringe. The autoclave was purged by three cycles of pressurization/venting with hydrogen (1 MPa), then pressurized with hydrogen (5 MPa), sealed and disconnected from the hydrogen source. The autoclave was pre-heated to the desired temperature (bath temperature) and the contents stirred. After the desired reaction time, the autoclave was cooled to room temperature, and the pressure slowly released. The reaction mixture was filtered through a plug of silica gel and then analyzed by GC. The crude product was purified by column chromatography.

Computational methods.

All DFT calculations were performed in Gaussian 09 using the M06L functional[19] and an ultrafine integration grid (99,590) in conjunction with the all-electron 6-31G(d,p) basis set for H and C atoms and the 6-31+G(d) basis set for all other non-metal atoms. The Stuttgart relativistic effective core potential basis set was used for the Ru (ECP28MWB)[20,21] atom. All structures were optimized in solvent by using the integral equation formalism polarizable continuum model (IEFPCM)[22] with radii and cavity-dispersion-solvent-structure terms in the SMD solvation model[23] for the experimental solvent of THF.

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Graphical for Table of Contents

Cooperative Interplay between a Flexible PNN-Ru(II) Complex and a $NaBH_4$ Additive in the Efficient Catalytic Hydrogenation of Esters

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