Cooperative Interplay between a Flexible PNN-Ru(II) Complex and a NaBH₄ 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(PPh₃)(CO) (PNN = 8-(2-diphenylphosphinoethyl)amidotrihydroquinoline), in combination with 5 mol% of NaBH₄, 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 NaBH₄ in the catalysis while the catalytically active species has been established as trans-dihydride [mer-PNN,N]RuH₂(CO) (PNN,N = 8-(2-diphenylphosphinoethyl)amidotrihydroquinoline). The stereo-structure of the PNN-N-ruthenium species greatly affects the activity of the catalyst, indeed the cis-dihydride isomer, [fac-PNN,N]RuH₂(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 LiAlH₄, NaBH₄ 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 esters5 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 Beller13 and others.14 Elsewhere highly active tetradentate PNNN15 and PNNP16 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(PPh₃)(CO) (PNN = 8-(2-diphenyl phosphinoethyl)amidotrihydroquinoline) (A, Chart 1) as a (pre-)catalyst for the hydrogenation of alky esters that operates efficiently under relatively mild conditions. On addition of NaBH₄ (5 mol%), A can hydrogenate a multitude of ester types incorporating...
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). 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>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Additive (mol%)</th>
<th>Time (h)</th>
<th>Conv. (%)</th>
</tr>
</thead>
<tbody>
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<td>1</td>
<td>A</td>
<td>none</td>
<td>24</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>A</td>
<td>t-BuOK (10)</td>
<td>24</td>
<td>35</td>
</tr>
<tr>
<td>3</td>
<td>A</td>
<td>NaBH₄ (5)</td>
<td>4</td>
<td>99</td>
</tr>
<tr>
<td>5</td>
<td>B</td>
<td>none</td>
<td>4/24</td>
<td>12/36</td>
</tr>
<tr>
<td>6</td>
<td>B</td>
<td>t-BuOK (10)</td>
<td>24</td>
<td>39</td>
</tr>
<tr>
<td>7</td>
<td>B</td>
<td>NaBH₄ (5)</td>
<td>3.5</td>
<td>99</td>
</tr>
<tr>
<td>8</td>
<td>C</td>
<td>NaBH₄ (5)</td>
<td>24</td>
<td>5</td>
</tr>
<tr>
<td>9</td>
<td>none</td>
<td>NaBH₄ (5)</td>
<td>24</td>
<td>1</td>
</tr>
</tbody>
</table>

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, H₂ = 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 NaBH₄ 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)(PPh₃)₂ (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.](image)

With a view to establishing the most compatible additive for the catalytic hydrogenation of 2a using A, six examples were screened namely, LiBH₄, NaBH₄, KBH₄, 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 NaBH₄ the standout performer. When the same amount of KBH₄ was employed, the rate of hydrogenation observed over 4 hours is notably less than that seen with NaBH₄. The reaction performed after 24 and 6 hours, respectively. On the other hand, with LiBH₄ (LiBH₄ is unstable and undergoes facile decompostion) as the additive only 36% of benzyl alcohol is produced after 36 hours. Among the different additives screened, NaBH₄ 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 NaBH₄ required for the hydrogenation of 2a using A, six differing amounts were screened under the same reaction conditions: 1 mol% NaBH₄, 2.5 mol% NaBH₄, 5 mol% NaBH₄ and 10 mol% NaBH₄ (Table 2). It was found that use of 5% mol of NaBH₄ gave the best conversion over the shortest time. By contrast, use of 1 and 2.5 mol% NaBH₄ did not
prove sufficient for a complete ester hydrogenation reaction (entries 1, 2), while use of 10 mol% gave no beneficial
catalytic efficiency when compared to that observed with 5 mol%
NaBH4 (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 MPa of H2) (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 benzy alcohol in high
yield (99%) after 4 hours.

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Time (h)</th>
<th>Conv.(%) by GC</th>
<th>TON</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me (2a)</td>
<td>4</td>
<td>99 (95[b])</td>
<td>1980</td>
</tr>
<tr>
<td>2</td>
<td>Et</td>
<td>12</td>
<td>99 (95[b])</td>
<td>1980</td>
</tr>
<tr>
<td>3</td>
<td>i-Pr</td>
<td>12</td>
<td>98 (94[b])</td>
<td>1960</td>
</tr>
<tr>
<td>4</td>
<td>n-Bu</td>
<td>12</td>
<td>97 (94[b])</td>
<td>1940</td>
</tr>
<tr>
<td>5</td>
<td>CH2:Ph</td>
<td>12</td>
<td>90 (85[b])</td>
<td>1800</td>
</tr>
<tr>
<td>6</td>
<td>t-Bu</td>
<td>24</td>
<td>10 (8[c])</td>
<td>200</td>
</tr>
</tbody>
</table>

[b] Conditions: alkyl benzoate (20 mmol), A (0.01 mmol), NaBH4 (0.2-2 mmol), THF (50 mL), H2 (5 MPa), T (120 °C). The conversion was determined by GC (n-tridecane as internal standard) with respect to benzy 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 mmol of A, 5 mol%
NaBH4 and under 5 MPa of hydrogen pressure at 120 °C in THF
(Table 3). While the Me, Et, i-Pr, n-Bu and CH2:Ph benzoates were
smoothly reduced to their corresponding benzy alcohol 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
NaBH4, 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/NaBH4 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, 2i, 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 NaBH4 or with the PNN-Ru
species, making A inactive toward ester reduction. 146

To further examine the substrate scope of A/NaBH4, 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/NaBH4 proved capable of hydrogenating a
wide selection of other esters (entries 7-9).

Table 2 Hydrogenation of methyl benzoate (2a) using different catalytic amounts of NaBH4

<table>
<thead>
<tr>
<th>Entry</th>
<th>NaBH4 (mol%)</th>
<th>H2 (MPa)</th>
<th>Time (h)</th>
<th>Conv.(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>5</td>
<td>12</td>
<td>25</td>
</tr>
<tr>
<td>2</td>
<td>2.5</td>
<td>5</td>
<td>12</td>
<td>56</td>
</tr>
<tr>
<td>3</td>
<td>5</td>
<td>5</td>
<td>4</td>
<td>99</td>
</tr>
<tr>
<td>4</td>
<td>10</td>
<td>5</td>
<td>1/3/3.5</td>
<td>24/90/99</td>
</tr>
</tbody>
</table>

[b] Conditions: methyl benzoate: 20 mmol, A (0.01 mmol), NaBH4 (0.2-2 mmol), THF (50 mL), H2 (5 MPa), T (120 °C). The conversion was determined by GC (n-tridecane as internal standard) with respect to benzyl alcohol. [c] Yield of the isolated product

Table 3. Reduction of alkyl benzoates by hydrogen in the presence of A

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>Time (h)</th>
<th>Conv.(%) by GC</th>
<th>TON</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me (2a)</td>
<td>4</td>
<td>99 (95[b])</td>
<td>1980</td>
</tr>
<tr>
<td>2</td>
<td>Et</td>
<td>12</td>
<td>99 (95[b])</td>
<td>1980</td>
</tr>
<tr>
<td>3</td>
<td>i-Pr</td>
<td>12</td>
<td>98 (94[b])</td>
<td>1960</td>
</tr>
<tr>
<td>4</td>
<td>n-Bu</td>
<td>12</td>
<td>97 (94[b])</td>
<td>1940</td>
</tr>
<tr>
<td>5</td>
<td>CH2:Ph</td>
<td>12</td>
<td>90 (85[b])</td>
<td>1800</td>
</tr>
<tr>
<td>6</td>
<td>t-Bu</td>
<td>24</td>
<td>10 (8[c])</td>
<td>200</td>
</tr>
</tbody>
</table>

[b] Conditions: alkyl benzoate (20 mmol), A (0.01 mmol), NaBH4 (1 mmol), THF (50 mL), H2 (5 MPa), T (120 °C). THF = tetrahydrofuran. [c] The presence of the bulky alkyl group.

To further examine the substrate scope of A/NaBH4, aliphatic
esters were also assessed (Table 5). It was found that once again
these more challenging esters could be smoothly reduced to their
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TON of 6560 (entry 1), while Me, Et, n-Pr and n-Bu acetates also
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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/NaBH4 proved capable of hydrogenating a
wide selection of other esters (entries 7-9).
Table 4. Reduction of various methyl benzoates \([2b – 2t]\) with different aryl group substitutions by hydrogen in the presence of A.\(^{[a]}\)

<table>
<thead>
<tr>
<th>Structure</th>
<th>Compound</th>
<th>S/C ratio</th>
<th>Time (h)</th>
<th>Conv. (%){(^{[c]})}</th>
<th>Yield (%){(^{[d]})}</th>
<th>TON</th>
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<tbody>
<tr>
<td>(\text{COOMe})</td>
<td>(2b (R = F))</td>
<td>2000</td>
<td>18</td>
<td>65</td>
<td>60</td>
<td>1300</td>
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<tr>
<td>(\text{COOMe})</td>
<td>(2c (R = \text{CF}_3))</td>
<td>8000</td>
<td>16</td>
<td>99</td>
<td>95</td>
<td>7920</td>
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<tr>
<td>(\text{COOMe})</td>
<td>(2d (R = Cl))</td>
<td>20000</td>
<td>28</td>
<td>85</td>
<td>82</td>
<td>17000</td>
</tr>
<tr>
<td>(\text{COOMe})</td>
<td>(2e (R = Br))</td>
<td>8000</td>
<td>12</td>
<td>93</td>
<td>85</td>
<td>1860</td>
</tr>
<tr>
<td>(\text{COOMe})</td>
<td>(2f (R = I))</td>
<td>2000</td>
<td>12</td>
<td>83</td>
<td>60</td>
<td>5200</td>
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<table>
<thead>
<tr>
<th>Structure</th>
<th>Compound</th>
<th>S/C ratio</th>
<th>Time (h)</th>
<th>Conv. (%){(^{[c]})}</th>
<th>Yield (%){(^{[d]})}</th>
<th>TON</th>
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<tbody>
<tr>
<td>(\text{COOMe})</td>
<td>(2g (R = F))</td>
<td>2000</td>
<td>12</td>
<td>97</td>
<td>93</td>
<td>1940</td>
</tr>
<tr>
<td>(\text{COOMe})</td>
<td>(2h (R = \text{CF}_3))</td>
<td>2000</td>
<td>5</td>
<td>99</td>
<td>94</td>
<td>1980</td>
</tr>
<tr>
<td>(\text{COOMe})</td>
<td>(2i (R = \text{Cl}))</td>
<td>100000(^{[b]})</td>
<td>30</td>
<td>48</td>
<td>42</td>
<td>48000</td>
</tr>
<tr>
<td>(\text{COOMe})</td>
<td>(2j (R = \text{Br}))</td>
<td>2000</td>
<td>8</td>
<td>95</td>
<td>90</td>
<td>1900</td>
</tr>
<tr>
<td>(\text{COOMe})</td>
<td>(2k (R = F))</td>
<td>20000</td>
<td>18</td>
<td>98</td>
<td>92</td>
<td>19600</td>
</tr>
<tr>
<td>(\text{COOMe})</td>
<td>(2l (R = \text{CF}_3))</td>
<td>16000</td>
<td>24</td>
<td>93</td>
<td>88</td>
<td>14880</td>
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<tr>
<td>(\text{COOMe})</td>
<td>(2m (R = \text{Cl}))</td>
<td>2000</td>
<td>8</td>
<td>99</td>
<td>93</td>
<td>1980</td>
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<tr>
<td>(\text{COOMe})</td>
<td>(2n (R = \text{Br}))</td>
<td>20000</td>
<td>24</td>
<td>92</td>
<td>85</td>
<td>18400</td>
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</table>

\(^{[a]}\) Conditions: substrate (20-200 mmol), A (0.05-0.001 mol%), NaBH\(_4\) (5-10 mol%), 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\(^{31}\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Ester</th>
<th>Alcohol</th>
<th>Time (h)</th>
<th>Conv. (%)(^{30})</th>
<th>TON</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>(\text{CF}_3)O (\text{O} \text{F}_3\text{C} \text{OH})</td>
<td>(\text{F}_2\text{C} \text{OH})</td>
<td>4</td>
<td>98</td>
<td>1960</td>
</tr>
<tr>
<td>2</td>
<td>(\text{O} \text{O} \text{OH})</td>
<td>(\text{OH})</td>
<td>8</td>
<td>97 (97(\text{d}))</td>
<td>1940</td>
</tr>
<tr>
<td>3</td>
<td>(\text{O} \text{O} \text{OH})</td>
<td>(\text{OH})</td>
<td>8</td>
<td>96</td>
<td>1920</td>
</tr>
<tr>
<td>4</td>
<td>(\text{O} \text{O} \text{OH})</td>
<td>(\text{OH})</td>
<td>12</td>
<td>95</td>
<td>1900</td>
</tr>
<tr>
<td>5</td>
<td>(\text{O} \text{O} \text{OH})</td>
<td>(\text{OH})</td>
<td>18</td>
<td>96</td>
<td>1920</td>
</tr>
<tr>
<td>6</td>
<td>(\text{O} \text{O} \text{OH})</td>
<td>(\text{OH})</td>
<td>24</td>
<td>14</td>
<td>280</td>
</tr>
<tr>
<td>7</td>
<td>(\text{O} \text{O} \text{OH})</td>
<td>(\text{OH})</td>
<td>12</td>
<td>91</td>
<td>1820</td>
</tr>
<tr>
<td>8</td>
<td>(\text{O} \text{O} \text{OH})</td>
<td>(\text{OH})</td>
<td>18</td>
<td>95</td>
<td>1900</td>
</tr>
<tr>
<td>9</td>
<td>(\text{O} \text{O} \text{OH})</td>
<td>(\text{OH})</td>
<td>24</td>
<td>75</td>
<td>1500</td>
</tr>
<tr>
<td>10</td>
<td>(\text{O} \text{O} \text{OH})</td>
<td>(\text{OH})</td>
<td>18</td>
<td>97 (87(\text{d}))</td>
<td>1940</td>
</tr>
</tbody>
</table>

\(^{30}\) Reaction conditions: substrate (20 mmol), A (0.01 mmol), NaBH\(_4\) (1 mmol), THF (50 mL), \(\text{H}_2\) (5 MPa), T (120 °C). THF = tetrahydrofuran.\(^{31}\) The conversion was determined by GC (n-tridecane as internal standard).\(^{32}\) Reaction conditions: substrate (80 mmol), F (0.01 mmol), S/C = 8000.\(^{33}\) 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 NaBH₄ 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-PN₃N]RuH(η¹-BH₃)(CO) (B in Chart 1) would be formed when A (in Chart 1) is treated with NaBH₄, as related η¹-BH₃ complexes have been prepared and reported as effective catalysts for the hydrogenation of esters by Kuriyama et al. and Beller. Indeed B can be isolated in reasonable yield on reaction of A with NaBH₄ in the presence of hydrogen gas, but was unexpectedly found to be an ineffective catalyst when employed in the absence of NaBH₄ (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, TSₐ,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 BH₄⁻,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 TS₁.6. 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 PN₃N ligand through transition state TS₅,7 and forms the hemiacetal intermediate 7. 1 → 6 → 7 is representative of an outer-sphere bifunctional mechanism6,7(a),(f),13(a),14(d).

Subsequently, the hemiacetal 7 returns a proton to the PNN ligand, rearranges and forms 8 via TS₇,8. The C-OMe bond in 8 is then broken through transition state TS₈,9 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)).16(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 H₂ activation or transfer hydrogenation with the NaBH₄ 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' → TS₅,1', see Fig. 54 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 NaBH₄ 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 NaBH₄ 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 NaBH₄ highlighted in the computational study, we additionally explored the conversion rates of methyl benzoate (20 mmol) using B i) in the absence of NaBH₄ (5 MPa H₂, T 120 °C), ii) with 0.05 equivalents of NaBH₄ (5 MPa H₂, T 120 °C and iii) with a stoichiometric amount of NaBH₄ (20 mmol) but no hydrogen (0 MPa H₂, T 120 °C). In the absence of hydrogen and in the presence of a stoichiometric amount of NaBH₄ B facilitates almost quantitative conversion of methyl benzoate in 3 hours. By contrast with 0.05 equivalents of NaBH₄ 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 NaBH₄ 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 NaBH₄ 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 NaBD₄ (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 ¹H 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 NaBH₄ participates in the overall transformation and supports the role of 5 mol% NaBH₄ in promoting the rate of hydrogenation. In another experiment the hydrogenation of benzaldehyde catalyzed by A/NaBH₄, 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 NaBH₄, 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: \(A \rightarrow B \) (isolated) → \(1' \rightarrow 1\). 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 NaBH₄ 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 spectroscopic shifts are relative to TMS (0.00 ppm) for 1H NMR spectra and relative to CDCl₃ (77.0 ppm) for 13C NMR spectra. Column chromatography was performed using silica gel (200 - 300 mesh). GC 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 NaBH₄) (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 functional¹⁹ 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 atom. All structures were optimized in solvent by using the integral equation formalism polarizable continuum model (IEPCM)²¹ with radii and cavity-dispersion-solvent-structure terms in the SMD solvation model²² for the experimental solvent of THF.

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**Notes and references**


Cooperative Interplay between a Flexible PNN-Ru(II) Complex and a NaBH₄ Additive in the Efficient Catalytic Hydrogenation of Esters

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\begin{align*}
\text{R}_1\overset{\text{O}}{\text{O}}\text{R}_2 & \xrightarrow{0.05\% - 0.001 \text{ mol} \% \text{ A}} 4 - 6 \text{ MP H}_2 / 5 \text{ mol\% NaBH}_4 \\
& \text{THF, 120-140 °C, 4-48 h} \\
& \text{TON up to 5000} \\
& \text{TOF up to 2000 h}^{-1} \\
& \text{60 - 99\% yield} \\
& \text{34 examples}
\end{align*}
\]