Ruthenium Catalysed Ester Reductions Applied to Pharmaceutical Intermediates

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ABSTRACT: Ruthenium pincer complexes were synthesised and used for catalytic ester reductions under mild conditions (~ 5 bar of hydrogen). An experimental design approach was used to optimise the conditions for yield, purity and robustness. Evidence for the catalytically active ruthenium dihydride species is presented. Observed intermediates and side-products as well as time-course data were used to build mechanistic insight. The optimised procedure was further demonstrated through scaled-up reductions of two pharmaceutically relevant esters, both in batch and in continuous flow.

KEYWORDS: *ester reduction, ruthenium catalysis, hydrogenation, CSTR flow, batch scale-up, mechanistic insight*

INTRODUCTION

Ester reductions are a staple functional group interconversion encountered throughout organic synthesis.[1, 2] For the purpose of small-scale syntheses, these are typically achieved using nucleophilic hydride reagents such as lithium aluminium hydride.[3] While these reagents are reliable, the process of handling and quenching these reagents is hazardous, and they generate significant waste streams often requiring specialist disposal, making them non-preferred for larger scale applications.[4] As such, this makes catalytic alternatives an attractive prospect. Catalytic homogeneous ester reductions have gained increased attention over the past two decades.[5] These have the advantages of being operable under milder conditions compared to those required by heterogenous reductions, and exhibit higher selectivity towards esters in the presence of other functional groups including alkenes and aromatic heterocycles.[5]

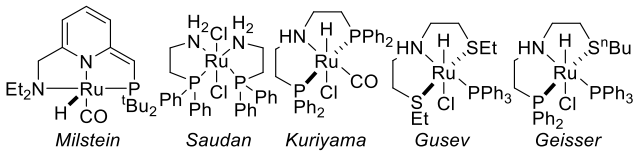


Figure 1. Catalysts for hydrogenation of esters.

Numerous reviews on this topic have been published.[5-10] Pioneering work in this field was done by Grey,[11] Teunissen and Elsevier[12] as well as Milstein and co-workers (Figure 1).[13] Since these findings, significant efforts within academia have been directed toward designing a wealth of catalyst systems based on ruthenium, iridium,[14] osmium,[15] rhenium[16] and increasingly base metals including iron,[17, 18] manganese[19, 20] and cobalt.[21] Extensive work has also been done within the fragrances and flavours industry with Geisser,[22] Kuriyama[4] and Saudan[23] having reported their own catalysts, these typically being ruthenium pincer complexes bearing an NH group.

These catalysts typically exploit "metal-ligand cooperation" as a means of heterolytically cleaving molecular hydrogen in order to achieve the desired reactivity.[24] A simplified mechanistic cycle is illustrated below (Figure 2). For more in depth mechanistic discussions, see work by Dub[25, 26] and Schaub.[27]

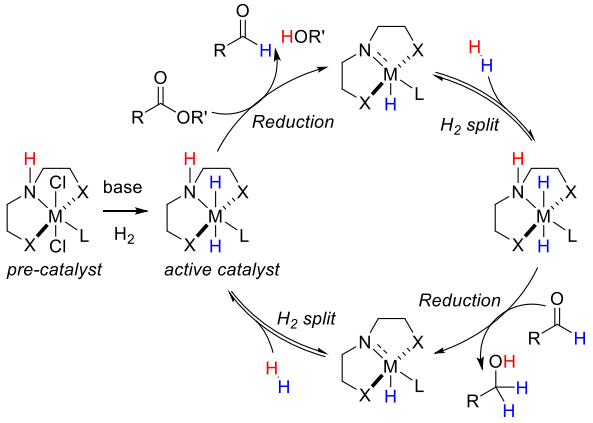


Figure 2. General catalytic cycle for ester hydrogenation.

Adoption of this technology within the pharmaceutical industry in contrast has been significantly slower, and metal hydride reagents are more typically employed.[2] The primary concerns are the high pressures of hydrogen required for these catalysts to operate efficiently as well as the limited functional group tolerance. The reduction of 2,2-difluoro-2-phenylacetate, an intermediate *en route* to a β-2-adrenergic receptor agonist has previously been achieved using Ru-MACHO under 20 bar of hydrogen enabled by use of a continuous flow reactor.[28] The issue of high pressure reductions has been addressed in a recent publication wherein a ruthenium pincer complex bearing a carbene ligand (**I**) was shown to reduce esters under particularly mild conditions.[29]

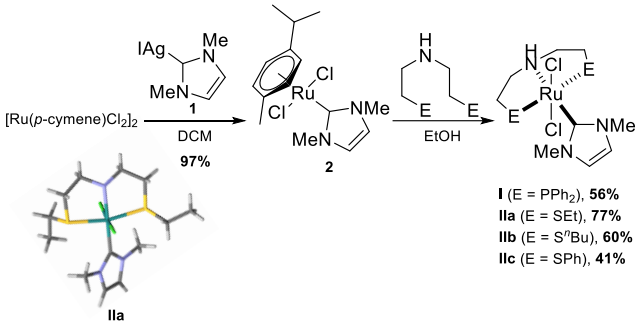
Herein, efforts toward understanding the applicability of this area of catalysis toward reduction of pharmaceutically relevant ester containing substrates are made. Mechanistic factors are discussed and the formation of by-products is ultimately suppressed using an experimental design approach. Finally, the reduction of two pharmaceutically relevant esters is demonstrated on large scale in batch and continuous flow.

RESULTS AND DISCUSSION

A variety of ruthenium catalysts were synthesised following modification of a procedure reported by Ogata, Kayaki and co-workers (scheme 1).[29] Reaction of commercially available [Ru(*p*-cymene)Cl_2] with silver carbene transfer reagent (**1**) afforded ruthenium carbene complex (**2**) in good yield. Substitution of the *p*-cymene ligand with a variety of tridentate ligands was achieved by heating these with complex **2** in ethanol. This allowed the formation of the reported Ru(PNP) complex (**I**) as well as three Ru(SNS) complexes. Ru(SNS) complexes bearing a PPh_3 ligand have previously shown to possess high activity by Gusev and coworkers.[30]

Ru(SNS) complexes **IIa, IIb** and **IIc** have not previously been reported, though a procedure for *in situ* generation of a Ru(SNS) complex bearing a carbene ligand has previously been suggested.[31] The meridional geometry of the ligand on Ru(diEtSNS) (**IIa**) was confirmed with a crystal structure. While the catalysts are air-sensitive in the solution state, they are stable to ambient conditions when dry.

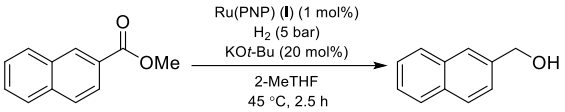
SCHEME 1. Synthesis of ruthenium pincer complexes.



Formation of the active dihydride complex was achieved by subjecting Ru(PNP) (**I**) to base and hydrogen in an NMR tube. A single new compound was observed by ^{31}P NMR with two hydride signals in the ^{1}H NMR [δ = –7.33 (td, J = 21.0, 9.5 Hz), –7.71 (td, J = 21.0, 9.5 Hz)], with chemical shifts and coupling constants comparable to those previously reported on related ruthenium complexes (full details in SI).[32]

Low pressures of hydrogen (5 bar) were employed when comparing the catalytic performance of the complexes as a means of making the conditions more accessible to hydrogenation vessels typically used within the pharmaceutical industry (Table 1). 2-MeTHF was employed as a more process-friendly alternative to THF (see SI for details).[33] KO*t*-Bu and KOMe were both found to efficiently promote the reaction, while sodium and lithium alkoxide bases, as well as organic bases did not (see SI for details).

TABLE 1. Comparison of the catalytic activity with respect to reduction of methyl 2-naphthoate.



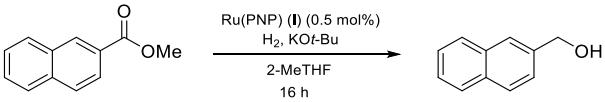
Catalyst	Yield[a]
I Ru(PNP)	96%
IIa Ru(diEtSNS)	93%
IIb Ru(di*n*-BuSNS)	95%
IIc Ru(diPhSNS)	72%

[a]Reaction conversion assessed by HPLC at 220 nm.

The model substrate, methyl 2-naphthoate was seen to reduce most cleanly with Ru(PNP) (**I**). Furthermore, examination of the gas-uptake curves revealed Ru(PNP) (**I**) to reduce the ester at the fastest rate. The Ru(SNS) complexes also had significantly longer induction periods. Accordingly, Ru(PNP) (**I**) was used for the remainder of this study.

In order to get a better understanding of how the robustness of the reaction outcome is affected by the continuous variables, an experimental design was conducted. A two-level, full factorial design with 4 centre points was run, wherein base loading, pressure, temperature and concentration were the parameters investigated (Table 2).

TABLE 2. Parameters for experimental design.



Parameter	Investigation range
Base	10-20 mol%
Hydrogen pressure	2-8 bar
Concentration	0.25-1.00 mol/L
Reaction temperature	30-60 °C

All reactions reached completion within 8 hours or less and good reproducibility was seen for the centre-point conditions (full details in SI). The temperature primarily affected the rate of reaction, with certain reactions going to completion in under an hour. Increased hydrogen pressure was beneficial, as this resulted in cleaner reaction profiles. Less starting material was observed, and formation of side-products, such as those formed through transesterification were disfavoured. The concentration and quantity of base were also found to affect the amount of hydrolysis which took place (figure 3). In particular, addition of less base and running reactions more concentrated diminished its formation. This is consistent with the inherent residual moisture content present within both the base and solvent on this scale.

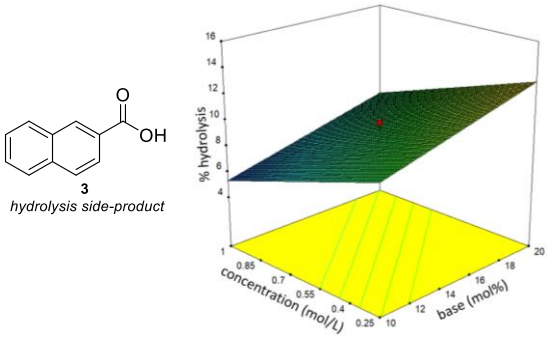
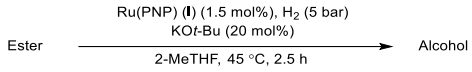
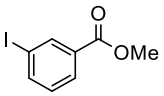
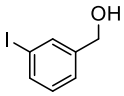
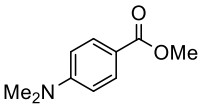
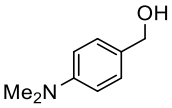
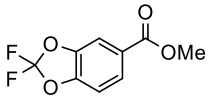
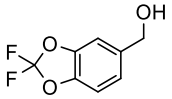
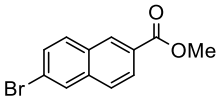
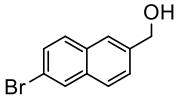
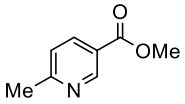
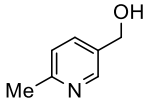
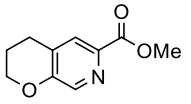
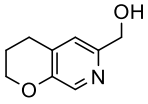


Figure 3. Surface response for hydrolysis side-product.

Following this, a number of different substrates were investigated to give a variety of pharmaceutically relevant primary alcohols (Table 3).[34-39] Labile C-I (entry 1) and C-Br (entry 4) bonds were shown to be preserved. Certain heterocycle containing esters, including pyridyl esters (entries 5 & 6) were tolerated. Other heterocycles, including thiazoles, isoxazoles and imidazoles in contrast remained unreactive. Nitro and nitrile containing compounds were also shown to preclude reactivity, even when higher catalyst loadings were employed (see SI for full list of substrates). Based on these findings, we envisage this transformation being most applicable to less functionally rich substrates.

TABLE 3. Substrates investigated.



Entry	Ester	Alcohol	%Conv.[a] (% yield)
1			>95 (66)[b]
2			75 (46)[b]
3			>90 (75)[b]
4			>95
5			>95 (79)[c]
6			>95 (62)[b]

[a]Reaction conversion assessed by HPLC at 220 nm.

[b]Isolated by flash chromatography

[c]Isolated by vacuum distillation

Interestingly, the anilino ester (entry 2) reduced particularly slowly, likely due to the reduced electrophilicity of the ester. In addition to the product alcohol, other intermediates including aldehyde were isolated from the reaction mixture (figure 4), providing evidence that at least in certain cases, aldehydes (or masked forms thereof) may be formed before reduction to the alcohol.

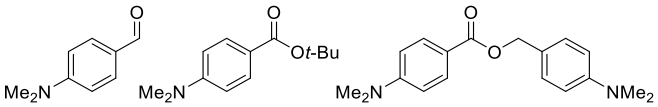


Figure 4. Isolated intermediates and by-products.

Intrigued by these observations we were interested in establishing what other side products are formed in this reaction. Monitoring the reduction of methyl benzoate by React IR revealed that before hydrogen is applied, a pre-equilibrium exists between the ester and the base, resulting in formation of *tert*-butyl benzoate (figure 5).

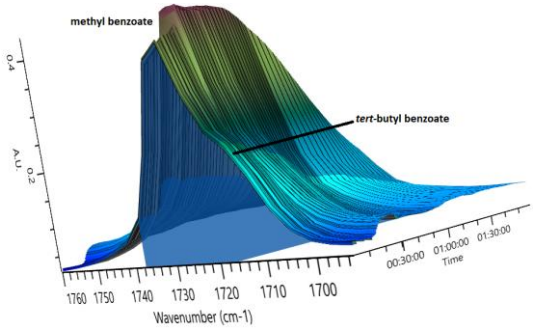


Figure 5. Formation of *tert*-butyl ester observed by IR.

In addition to this, irreversible hydrolysis also takes place (figure 6). During the reduction of methyl benzoate, benzaldehyde was not directly observed. This suggests for this particular substrate that benzaldehyde only formed either transiently or masked as a hemiacetal or indeed in its hydrated form. Benzyl benzoate, while known to form under these conditions, could not be differentiated from the SM by React IR.

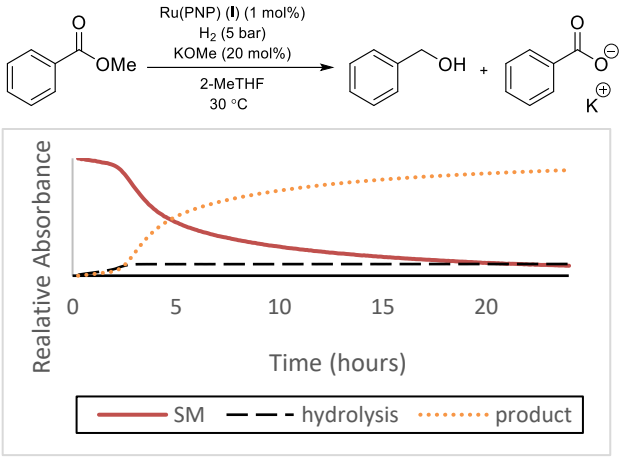
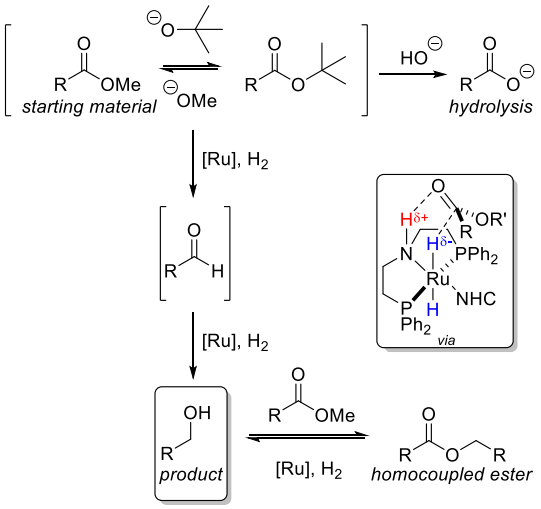


Figure 6. React IR time-course reduction of methyl benzoate.

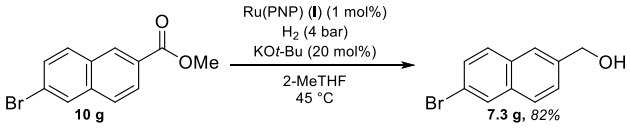
In addition, a temperature dependent induction was observable, whereby the end of the induction period also coincided with formation of the hydrolysis product plateauing. This strongly suggests the induction period to be directly linked with the consumption of adventitious water. Water has indeed previously been shown to inhibit activity in related catalytic systems.[32] Addition of 20 mol% of potassium benzoate showed no deleterious effect on conversion.

Based on the previous observations, the following scheme depicts the proposed fate of the ester substrate (scheme 2). During the induction period, hydrolysis and transesterification with the base take place. Upon formation of the active catalytic species, reduction of either ester takes place. This initially forms an aldehyde, possibly as a short lived intermediate, or masked as a hemiacetal or hydrate, and then further reduced to the product alcohol. The product may then undergo transesterification with the starting material to give a homocoupled ester; this too, given enough time may reduce to the product alcohol. With the exception of the hydrolysis side-product, all other substrates eventually react to give the product.



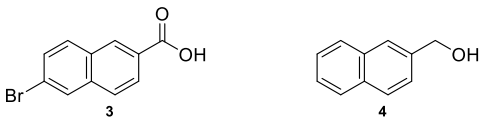
SCHEME 2. Fate of ester.

With this knowledge in hand, two of the previously identified pharmaceutically relevant intermediates were considered for further examination. Firstly, the reduction of methyl 6-bromo-2-naphthoate[37] was performed on a 10 g scale (scheme 3).



SCHEME 3. Reduction of methyl 6-bromo-2-naphthaote.

The reaction was run in 500 mL glass jacketed vessel. Solids were observed to precipitate out of solution as the reaction proceeded, presumably due to the product alcohol being less soluble in the reaction solvent, 2-MeTHF than the SM. The reaction was left overnight, after which the rate of gas consumption had plateaued. At this stage the reaction mixture was sampled, and complete consumption of SM was indicated. Isolation of the product was performed by an aqueous extraction, followed by a put-and-take distillation with addition of isooctane. Compared to the existing process in which the reduction was performed with DIBAL-H, the isolation procedure was significantly simplified. No issues with exotherms or formation of emulsions took place during the work-up while achieving a similar PMI.[37] Furthermore, the composition of the resulting waste streams was more favourable. In addition to the desired product, hydrolysis side-product (**3**) and desbromo side-product (**4**) were observed by HPLC as low-level impurities.



SCHEME 4. Isolated side products from reduction of methyl 6-bromo-2-naphthoate.

The hydrolysis by-product (**3**) formed while affecting the yield was readily removed by performing a basic wash. The desbromo side-product (**4**), thought to form as a result of trace palladium present in the vessel was not readily purged.

Following on from this, we investigated transferring the hydrogenation of methyl 6-bromo-2-naphthoate to a continuous flow reactor. The potential benefits of this would be to allow access to higher temperatures/pressures in a safer manner, should this be necessary as a means of intensifying the process. The key challenge to overcome based on previous batch observations was the issue of solids being generated over the course of the reaction which would likely block conventional tubing or capillaries. As such a bespoke CSTR flow reactor available from Autichem Ltd. was examined with the following set-up (figure 7).

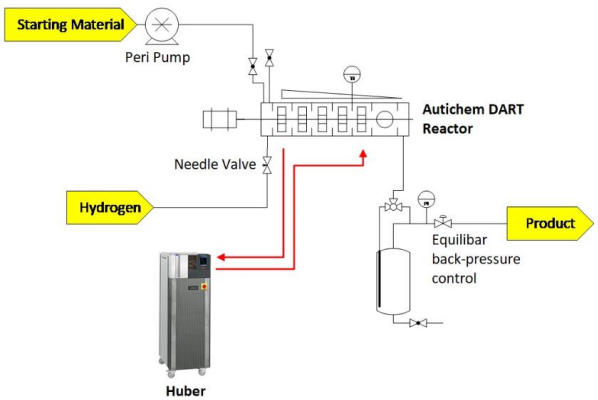


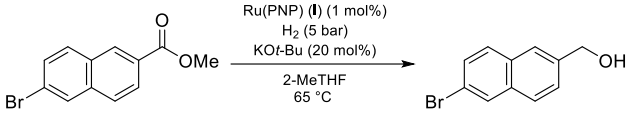
Figure 7. Schematic of CSTR flow set-up.

The two inputs into the reactor are hydrogen gas and the reaction mixture consisting of the methyl 6-bromo-2-naphthoate, KO*t*-Bu, Ru(PNP) (**I**) and 2-MeTHF, which were made up in a feed. As the liquid phase enters the reactor, the rotating agitator ensured efficient gas-liquid contact. The rate at which the mixture was pumped, gave control over the residence time. In addition to giving plug-flow like behavior, this set-up has the added benefit of having a greater tolerance for solids as the agitator helped mobilise slurries.

Initial runs resulted in no conversion, as the KO*t*-Bu had settled within the feed tank in which the reaction mixture was made up, and thus did not enter the reactor. This issue was resolved by replacing solid KO*t*-Bu with a KO*t*-Bu as a solution in THF, to give a homogeneous feed solution. The results from the runs following this are summarised below (Table 4).

The set-up was operationally straightforward, and worked with minimal complications to afford a suspension of product. Long residence times were required to achieve high conversions. The longest residence time (54 mins) would allow 50 g of substrate to be reduced in ~17 h. While the reactor itself was rated to higher temperatures and pressures, other components in this particular set-up were rated to a maximum of 7 bar of pressure. Throughput could in principle be increased by applying higher temperatures and pressures. Furthermore, larger variants of these reactors are commercially available.

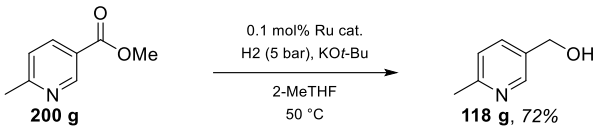
TABLE 4. Results from CSTR flow reactor.



Residence time (mins)	Conversion[a]
54	90
23	65
12	38

[a]Reaction conversion assessed by HPLC at 220 nm.

Following on from this, we focused our attention on the large scale reduction of methyl 6-methylnicotinate, another pharmaceutically relevant intermediate (scheme 5).[39] The reaction was performed in a 5 L Hastelloy pressure reactor equipped with a gas-entrainment impeller. A lower catalyst loading (0.1 mol%) was used without loss of activity.



SCHEME 5. Scaled-up reduction of methyl 6-methylnicotinate

After an initial induction period of about 15 mins, the reaction proceeded very quickly, and of the 50 L of hydrogen gas uptake measure in total, 47 L were consumed within the first 1.5 hours. During this time, the highest recorded temperature was 53 °C, 3 °C above the jacket temperature. This reflected insignificant exothermic activity, and no additional restrictions on the feed-rate of hydrogen gas were deemed necessary at this scale. Once the reaction had reached completion, the solvent was distilled off and the product was isolated by vacuum distillation using a wiped film evaporator. In addition to effectively purging the less volatile hydrolysis product, 6-methylnicotinic acid, this also reduced the level of residual ruthenium to 10 ppm. Compared to an existing $LiAlH_4$ process,[39] a significantly improved PMI was achieved (20 vs. 190), and may be further improved by reducing the mechanical losses which occurred during the isolation process. This improved PMI is both a reflection of employing a catalytic rather than a stoichiometric method, as well as less solvent being required for the quench and work-up of the reaction. Further to this, the waste stream consisted of residues enriched in ruthenium which could be sent directly for metal recovery.

CONCLUSION

In summary, the catalytic reduction of pharmaceutically relevant esters using low hydrogen pressures has been demonstrated. Both batch and continuous flow set-ups have been utilised, the former benefitting from being amenable for transfer into multi-purpose hydrogenation vessels and the latter benefitting from the potential for higher throughput. The work-up procedures and isolations were simplified compared to corresponding metal hydride mediated reductions, and aqueous aluminum containing waste streams were avoided. In the case of the reduction of methyl 6-methylnicotinate, a significantly improved PMI was also obtained. Work is ongoing as assess other pharmaceutically relevant substrates, as well as transferring hydrogenations to a high-pressure segmented flow reactor.

EXPERIMENTAL

Large-Scale batch reduction of methyl 6-bromo-2-naphthoate

To a 500 mL Ecoclave equipped with a gas entrainment impeller was added methyl 6-bromo-2-naphthoate (10 g, 38 mmol, 1.0 eq.) and Ru(PNP) (**I**) (268 mg, 0.377 mmol, 0.01 eq.). The vessel was left to purge with nitrogen for 5 mins before adding 2-MeTHF (100 mL) and potassium *tert*-butoxide (847 mg, 7.54 mmol, 0.20 eq.). The vessel was sealed and the impeller was set to stir at 300 rpm. The vessel was pressurised with nitrogen (3.5 bar) then vented (x3), then pressurised with hydrogen (3.5 bar) then vented. The vessel was then pressurised and maintained with hydrogen (4.0 bar). The jacket of the vessel was heated to 45 °C, the impeller was set to 700 rpm and the mixture was left in this state for 4 h. Analysis by HPLC indicated > 99% conversion. 1 M aqueous hydrochloric acid (100 mL) was added and the mixture was stirred at 1000 rpm for 10 mins. The organic phase was separated and passed through a silica plug (16 g, 2.5 cm). The solvent was removed by distillation while continually adding isooctane (90 mL). Following this the mixture was cooled in an ice bath. The precipitated solids were collected by filtration and dried under reduced pressure to afford product as a pale yellow powder (7.3 g, 31 mmol, 82%).**^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.00 (d, 1H, *J* = 1.5 Hz, ArH), 7.79 (s, 1H, ArH), 7.75 (d, 1H, *J* = 8.5 Hz), 7.71 (d, 1H, *J* = 8.5 Hz), 7.56 (dd, 1H, *J* = 8.5, 2.0 Hz, ArH), 7.51 (dd, 1H, *J* = 8.5, 1.5 Hz, ArH), 4.86 (s, 2H, CH_2O), 1.80 (br. s, 1H, OH); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 139.0, 134.1, 132.0, 129.9, 129.74, 129.68, 127.6, 126.3, 125.4, 120.0, 65.4.

Large-Scale reduction of methyl 6-bromo-2-naphthoate in continuous flow

A stirred feed-tank was charged with Ru(PNP) (**I**) (668 mg, 0.941 mmol, 0.005 eq.), methyl 6-bromo-2-naphthoate (50 g, 189 mmol, 1 eq.), potassium *tert*-butoxide (38 mL, 38

mmol, 1 M in THF) and 2-MeTHF (500 mL) while maintaining a nitrogen atmosphere.

Through an Autichem CSTR flow reactor was pumped the reaction mixture while also being supplied with hydrogen gas (5 bar). The jacket of the reactor was set to 65 °C and the agitator was set to 219 rpm. The residence time of the reaction mixture was varied by altering the rate at which the mixture was pumped (54, 23 and 12 mins). The reaction was left the reach a steady state before directly sampling the resulting reaction mixture for analysis.

Large-scale batch reduction of methyl 6-methyl nicotinate

To a 5 L Büchi Kiloclave equipped with a gas entrainment impeller was added methyl 6-methylnicotinate (200 g, 1.32 mol, 1.0 eq.), Ru(PNP) (I) (937 mg, 1.32 mmol, 0.0010 eq.), potassium *tert*-butoxide (29.7 g, 265 mmol, 0.20 eq.) and 2-MeTHF (2.5 L). The vessel was sealed and purged with nitrogen (3 x 3 bar), then hydrogen (3 x 2.5 bar) before filled and maintained with hydrogen (2.8 bar). The jacket temperature was set to 50 °C and the impeller was set to 750 rpm. After 1.5 h, the hydrogen pressure was increased (5 bar) and left to stir overnight. The jacket temperature was set to 20 °C, the hydrogen was released and the vessel was purged with nitrogen (3 x 5 bar). HPLC analysis indicated > 98% conversion. Saturated ammonium chloride solution (30 mL) was added, and the solvent was distilled off under reduced pressure. To product was then isolated by vacuum distillation (100 °C, 0.7 mbar) to afford product as a yellow solid (118 g, 955 mmol, 72%). **^{1}H NMR** (400 MHz, $CDCl_3$): δ 8.34 (s, 1H, NCH), 7.59 (dd, 1H, *J* = 8.0, 2.0 Hz, NCCHC*H*), 7.12 (d, 1H, *J* = 8.0 Hz, NCCH). 4.64 (s, 2H, CH_2), 3.77 (br. s, 1H, OH), 2.50 (s, 3H, CH_3); **^{13}C NMR** (101 MHz, $CDCl_3$): δ 157.5, 147.8, 136.7, 133.8, 123.3, 62.4, 24.0.

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Author Contributions

Experimental work was performed by Y. Shaalan. The manuscript was written through contributions of all the authors. All of the authors approve the final version of the manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

SUPPLEMENTARY INFORMATION

The Supporting Information is available free of charge on the ACS Publications website.

Experimental procedures, characterisation of compounds, PMI calculations and further details of DoE studies included.

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