Heterogeneous Hydrogenation of Esters Under Mild Conditions via Solid-Supported Phosphorus-Ru Catalysts

Frank J. L. Heutz, Christina Erken, Mae Joanne B. Aguila, Laurent Lefort and Paul C. J. Kamer*

Abstract: The catalytic reduction of esters using H_2 offers a more sustainable alternative compared to classic stoichiometric reagents. Nowadays a wide range of highly efficient homogeneous catalysts are known, but these suffer from poor catalyst recoverability. Therefore, most industrial applications are based on heterogeneous catalysts but these processes are generally operated under harsh conditions (>200 °C, >100 bar). Here we describe the first catalytic system which combines the activity of homogeneous catalysts with the recoverability of a heterogeneous catalyst. The presented system is capable of hydrogenating esters under very mild conditions (25 °C, 50 bar) and could easily be recovered. The catalyst is based on phosphorus ligands covalently attached to a polymeric support and could be readily obtained via a facile solid-phase synthetic protocol in high yields with minimal work-up.

The reduction of esters to the corresponding alcohols is one of the key transformations in organic chemistry. On laboratory and fine-chemical scale stoichiometric hydride reagents such as $LiAlH_4$ and $NaBH_4$ are commonly employed. While these reagents are relatively cheap they can be hazardous to handle and generate stoichiometric amounts of waste.[1] A more economical and environmentally benign approach is the catalytic conversion of esters using H_2, yielding the desired alcohols as the sole products.[2]

Industrially the catalytic hydrogenation of esters is applied for the production of long chain alcohols which are important intermediates; for example in the production of surfactants and plasticizers.[3] Typically, heterogeneous copper chromite catalysts are employed leading to high alcohol yields. These types of catalysts however, operate under severe conditions (250-350℃ at 100-200 bar) compatible with only a limited set of functional groups.[4] Arene reduction for example, often presents a big problem with heterogeneous catalysts. Moreover, when considering the toxicity of Cr compounds and the high capital and operational costs associated with high pressure units, it is no surprise that such heterogeneous catalysts have not been used in the production of fine chemicals or pharmaceuticals. Hence there has been a strong drive from both academia and industry in the past decades to develop homogeneous systems capable of these transformations under milder conditions. Since pivotal work in 2006 from both the Millstein group[5] (complex **I**) and Saudan *et al*.[6] (complex **II**) numerous catalysts capable of ester reduction under milder conditions have been reported (40-150 °C and 10-50 bar, see fig. 1).[7]

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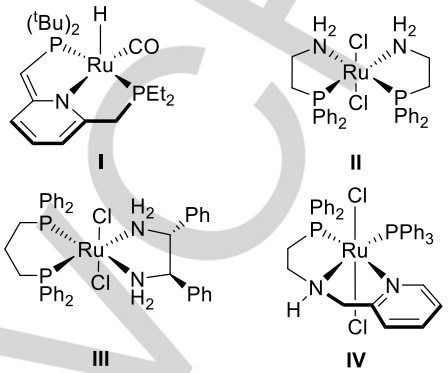


Figure 1. Selected representative homogeneous ester hydrogenation catalysts.

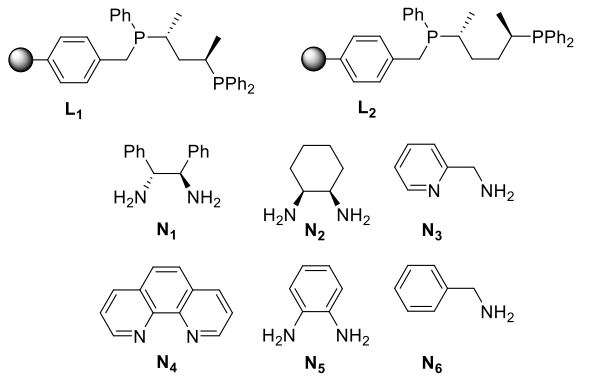
However, these homogeneous systems suffer from problematic recovery and recycling of the often expensive transition metal and ligand.[8] Also, the bi- or multidentate PN-ligands commonly employed are synthesized via multiple steps that can be low yielding in part due to troublesome work-up procedures. The synthesis of the PN-ligands via solid-phase synthesis is an attractive alternative affording the desired ligands in high yield with minimal work-up.[9] Additionally, ligands covalently bound to a solid-support provide immobilized homogeneous catalysts which facilitates recycling. Recently we reported on the solid-phase synthesis of recyclable supported diphosphine[10] and phosphine-phosphite ligands[11] and their application in asymmetric hydrogenation. In this work we demonstrate a new solid-phase synthetic methodology for the preparation of supported PN and PNN ligands and their application in the Ru-catalyzed hydrogenation of esters under mild conditions.

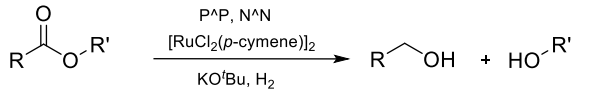
The application of Noyori-type ruthenium BINAP/diamine catalyst systems in ester hydrogenation has been investigated by various groups.[12] Recently, Kuriyama *et al.* at Takasago demonstrated that BINAP can be substituted with cheaper bidentate phosphorus ligands such as 1,3-bis(diphenylphosphino)propane (dppp) (complex **III**, fig. 1).[13] Inspired by this work two immobilized diphosphines ($\mathbf{L_1}$ and $\mathbf{L_2}$, table 1) previously published, were tested as supported ligands in ester hydrogenation. Both diphosphines were combined with 6 different amines ($\mathbf{N_1}$-$\mathbf{N_6}$) and two Ru precursors, ($RuCl_2(PPh_3)_3$ and $[Ru(p\text{-cymene})Cl_2]_2$). The generated small library of 24 members was tested in the hydrogenation of two substrates, i.e. methyl benzoate ($\mathbf{S_1}$) and methyl hexanoate ($\mathbf{S_2}$) in presence of KO^{t}Bu as an activator. The most important results of this screening are depicted in table 1 (see ESI for full results).

The combination of $\mathbf{L_1}$, bearing a C3 backbone, with (*S*,*S*)-DPEN ($\mathbf{N_1}$) and $[Ru(p\text{-cymene})Cl_2]_2$ gave the best results, which is in agreement with results from Kuriyama *et al.* who used a combination of the analogous dppp ligand with (*S*,*S*)-DPEN.[13] We observed a conversion of 80% and a selectivity of 96% towards the desired alcohol for methyl benzoate ($\mathbf{S_1}$, entry 1).

For methyl hexanoate (**S₂**) lower conversions were obtained (entry 3). Supported diphosphine **L₂** with a C4 backbone gave lower activity and selectivity, which is consistent with literature (see entries 2-4). Of all the other amines tested only **N₂** showed notable conversions (entries 5-6). With the other Ru precursor, $Ru(PPh_3)_3Cl_2$, lower conversions were obtained (See ESI).

Table 1. Reduction of esters using supported ligands (**L₁** and **L₂**) and amines.



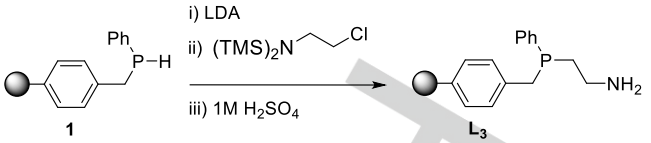


S₁: R = Ph, R' = Me
S₂: R = C_5H_{11}, R' = Me

Entry[a]	P^P	N^N	Substrate	Conversion [%][b]	Selectivity [%][c]
1	**L₁**	**N₁**	**S₁**	80	96
2	**L₂**	**N₁**	**S₁**	37	75
3	**L₁**	**N₁**	**S₂**	39	47
4	**L₂**	**N₁**	**S₂**	15	21
5	**L₁**	**N₂**	**S₁**	44	81
6	**L₂**	**N₂**	**S₁**	20	55

[a] Conditions: 0.5 mmol substrate, 1.0 mol% of ligand and amine, 0.9 mol% Ru metal, 10 mol% KO^tBu, 2.5 mL of THF, 80 °C, 50 bar H_2., 16 h. [b] Conversion of starting ester determined by GC. [c] Selectivity towards the desired alcohol.

Encouraged by these positive preliminary results we set out to develop more active resin-supported ester hydrogenation catalysts. The first synthetic target was an immobilized analogue of the aminophosphane ligand successfully employed by Saudan *et al.* in ester hydrogenation (complex **III**, fig 1.). The corresponding bis(aminophosphane) ruthenium complex showed high activity in the reduction of esters (TOF = 2200 h^{-1}).[6c, 6d] Various procedures for synthesizing aminophosphane ligands have been reported and an adaptation of the method developed by Abdur-Rashid *et al*. was used to synthesize the analogous supported ligand.[14]



Scheme 1. Synthesis of supported aminophosphane ligand **L₃**.

The starting point of the solid-phase synthesis is supported phosphine (**1**) which can be readily obtained by treating a chloromethyl functionalized resin, here Merrifield resin, with lithium phenylphosphide.[10] Subsequently the phosphine moiety was lithiated using lithium diisopropylamine (LDA) yielding the desired supported lithium phosphide (see scheme 1). This was confirmed using gel-phase NMR. In addition to a small shift of 3 ppm, the lithiation led to major peak broadening in ^{31}P NMR (fig. 2) while a single sharp peak at δ = 0.4 ppm was observed by ^{7}Li NMR.

Next the ligand backbone was introduced by reaction of lithiated species **Li·1** with a trimethylsilyl (TMS) protected chloroamine. Successful incorporation of the ligand backbone was confirmed using ^{31}P NMR spectroscopy with the desired product exhibiting a single peak at δ = -23.7 ppm. Removal of the TMS groups was achieved by treatment with dilute sulfuric acid. Upon hydrolysis a small upfield shift of approximately 1 ppm was observed corresponding to the desired supported aminophosphane **L₃** (δ = -24.8 ppm). Moreover, complete hydrolysis could also be confirmed by monitoring the disappearance of the distinctive TMS peak by gel-phase ^{13}C NMR and the observation of primary amine stretch frequencies using FT-IR spectroscopy. The supported ligand was obtained in near quantitative yield with minimal workup demonstrating the power of solid-phase synthesis. The phosphorus loading was determined using elemental analysis.

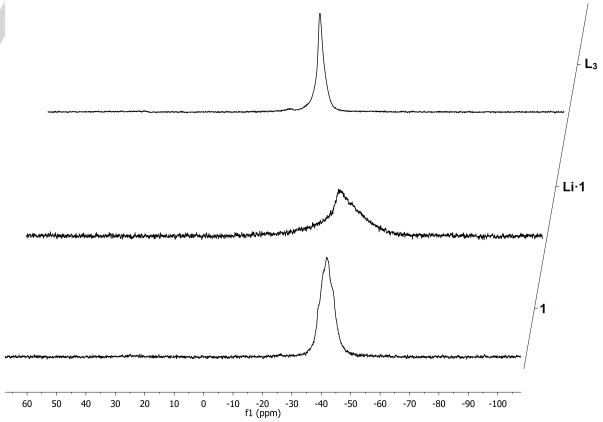


Figure 2. Solid-phase synthesis of supported aminophosphane **L₃** monitored by gel-phase ^{31}P NMR.

Supported aminophosphane **L₃** was then applied in the hydrogenation of methyl benzoate (**S₁**) and methyl hexanoate (**S₂**) using two Ru-precursors (see table 2). Full conversion of **S₁** with over 99% selectivity to the desired alcohol was achieved with both metal precursors at 100 °C and 50 bar H_2 (entries 1-2). For the alkyl ester (**S₂**) however, only modest conversions up to 52% could be achieved (entries 3-4) with a significant amount of hexyl hexanoate formed via transesterification between the

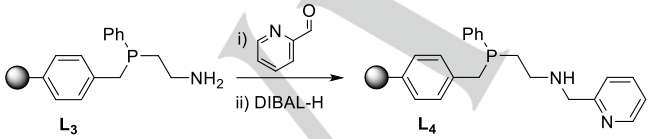
product and starting material. For **S_1** the desired product could even be obtained in full yield at a decreased temperature of 80 °C (entry 5). Interestingly, complex **II** reported by Firmenich[6] contains two PN ligands, while our Ru species is only monoligated demonstrating that ester hydrogenation activity does not necessarily require two PN ligands per Ru.

Table 2. Reduction of esters using supported aminophosphane **L_3**.

Entry[a]	Ru	Substrate	Conversion [%][b]	Selectivity [%][c]
1	$RuCl_2(PPh_3)_3$	**S_1**	>99	>99
2	$[Ru(p\text{-cymene})Cl_2]_2$	**S_1**	>99	>99
3	$RuCl_2(PPh_3)_3$	**S_2**	52	64
4	$[Ru(p\text{-cymene})Cl_2]_2$	**S_2**	47	59
5[d]	$RuCl_2(PPh_3)_3$	**S_1**	>99	>99
6[d]	$[Ru(p\text{-cymene})Cl_2]_2$	**S_1**	95	>99

[a] Conditions: 0.25 mmol substrate, 1.0 mol% ligand, 0.9 mol% Ru metal, 10 mol% KO^{t}Bu, 1 mL THF, 100 °C, 50 bar H_2, 16 h. [b] Conversion of starting ester determined by GC. [c] Selectivity towards the desired alcohol. [d] Performed at 80 °C.

In order to further improve the activity of these supported ester hydrogenation catalysts we turned towards supported PNN ligands. Research by Gusev *et al.* showed that ruthenium PNN complexes (see complex **IV**, fig. 1) can be highly effective ester hydrogenation catalysts for both aromatic and alkyl esters at temperatures as low as 40 °C.[15] The analogous supported PNN ligand can be readily obtained by further modification of immobilized aminophosphane **L_3** via a condensation reaction with 2-pyridinecarboxaldehyde (Scheme 2). The formed imine exhibited a peak at δ = -22.7 ppm in the ^{31}P NMR spectrum and the introduction of the 2-picoline moiety was confirmed using FT-IR. Subsequently the imine was reduced using diisobutylaluminum hydride (DIBAL-H). The desired supported PNN ligand **L_4** was obtained in high yield (88%) with minimal workup and shows a ^{31}P NMR shift of δ = -23.9 ppm. The complete reduction of the imine was confirmed using gel-phase ^{13}C NMR where a new peak at δ = 55.0 was observed corresponding to the NCH_2 carbon. The phosphorus loading was determined using elemental analysis.



Scheme 2. Solid-phase synthesis of supported PNN ligand **L_4**.

Supported PNN-ligand **L_4** was screened in the hydrogenation of **S_1** and **S_2**. Using a combination of ligand **L_4** and $RuCl_2(PPh_3)_3$ 100% yield towards the desired alcohol was obtained for both substrates at 40 °C (entries 1 and 2, table 3). Even at temperatures as low as 25 °C almost full conversion and selectivity was achieved (entries 5 and 6). To our knowledge, these conditions are the mildest ever reported for a supported ester hydrogenation catalyst. Using the $[Ru(p\text{-cymene})Cl_2]_2$ precursor however, only conversions up to 60% were obtained (entries 3-4).

Table 3. Reduction of esters using supported PNN-ligand **L_4**.

Entry[a]	Ru	Substrate	Conversion [%][b]	Selectivity [%][c]
1	$RuCl_2(PPh_3)_3$	**S_1**	>99	>99
2	$RuCl_2(PPh_3)_3$	**S_2**	>99	>99
3	$[Ru(p\text{-cymene})Cl_2]_2$	**S_1**	59	91
4	$[Ru(p\text{-cymene})Cl_2]_2$	**S_2**	50	61
5[d]	$RuCl_2(PPh_3)_3$	**S_1**	99	>99
6[d]	$RuCl_2(PPh_3)_3$	**S_2**	97	99

[a] Conditions: 0.25 mmol substrate, 1.0 mol% ligand, 0.9 mol% Ru metal, 10 mol% KO^{t}Bu, 1 mL THF, 40 °C, 50 bar H_2, 16 h. [b] Conversion of starting ester determined by GC. [c] Selectivity towards the desired alcohol. [d] Performed at 25 °C.

The best performing catalyst based on **L_4** and $RuCl_2(PPh_3)_3$ was employed to determine the substrate scope. Especially alkyl esters seemed to be hydrogenated with relative ease, achieving almost full conversion and selectivity for both ethyl hexanoate (**S_3**) and hexyl hexanoate (**S_4**). Methyl cyclohexanoate (**S_5**) proved to be a more challenging substrate and only 73% conversion and 82% selectivity to the desired product was reached. Interestingly, no conversion was observed for diethyl succinate **S_6** even at increased reaction times and temperatures up to 100 °C. Aromatic esters **S_7** and **S_8** also proved more challenging. For both substrates moderate conversion was reached at 40 °C. However, at an increased temperature of 60 °C almost full conversion was obtained for both substrates.

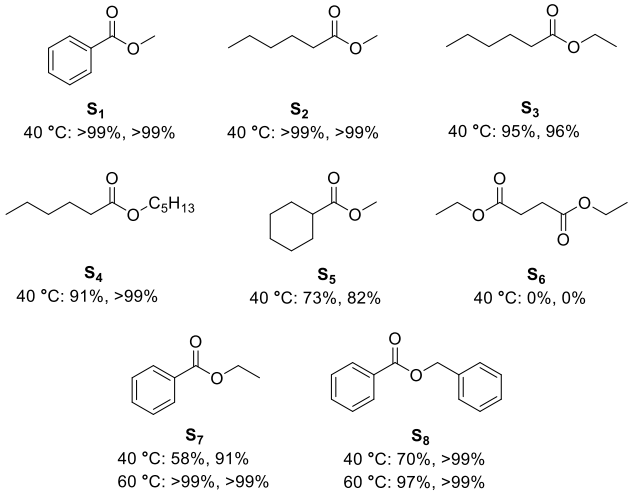


Figure 3. Substrate scope for ester hydrogenation using supported ligand **L_4** (conversion and selectivity indicated below structures). For conditions see table 3.

Table 4. Results for the recycling of ligand L_4 in the hydrogenation of S_1.

Run[a]	Ru	Substrate	Conversion [%][b]	Selectivity [%][c]
1	$RuCl_2(PPh_3)_3$	S_1	69	95
2	$RuCl_2(PPh_3)_3$	S_1	72	93
3	$RuCl_2(PPh_3)_3$	S_1	69	93
4	$RuCl_2(PPh_3)_3$	S_1	47	89

[a] Conditions: 0.25 mmol substrate, 1.0 mol% ligand, 0.9 mol% Ru metal, 10 mol% KO^{t}Bu, 1 mL THF, 40 °C, 50 bar H_2 2 h. [b] Conversion of starting ester determined by GC. [c] Selectivity towards the desired alcohol.

Finally the reusability of the solid-supported L_4 based system was investigated. Shorter reaction times (2h instead of 16h) were used in order to assess any decrease in the rates of the reaction. Supported PNN-Ligand L_4 could successfully be used up to 3 times in the hydrogenation of S_1 without loss of activity. After each run the supernatant was removed and fresh substrate and base solutions were added, all under a flow of H_2 to ensure catalyst stability. After the 4th run some catalyst deactivation was observed, possibly caused by the introduction of trace amounts of water or oxygen during the catalyst work-up. Moreover, the presence of both substrate and H_2 was found to be crucial for catalyst stability hampering further efficient recycling in the used batch setup. These preliminary results however do demonstrate that the supported catalyst can be easily recovered and reused using a simple filtration step. This catalytic system would be very suitable for application of ester hydrogenation in a continuous flow system.

In summary, we have prepared the first heterogeneous catalyst able to hydrogenate esters at room temperature. For this purpose, we developed an efficient solid-phase synthetic methodology for the preparation of supported PN and PNN ligands in high yield and purity. After addition of a Ru precursor, these catalytic systems were able to hydrogenate a range of aromatic and alkyl esters at temperatures as low as 25 °C. High conversion and selectivity were achieved without any observable arene reduction. Preliminary recyclability tests were performed demonstrating that the supported catalyst could be easily recovered and reused. Currently work is ongoing to extend both the supported ligand library as well as the substrate scope. Also, the possibility to use these immobilized ester hydrogenation catalysts under flow conditions will be explored.

Acknowledgements

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Keywords: catalyst immobilization • ester reduction • hydrogenation • N,P ligands • solid-phase synthesis

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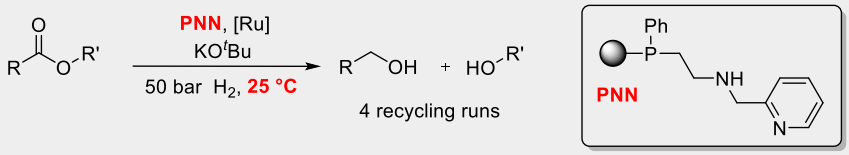

Heterogeneous ester hydrogenation Here we describe the first heterogeneous catalyst capable of hydrogenating esters under very mild conditions (25 °C, 50 bar). Additionally easy catalyst recovery and recycling was achieved. The system is based on phosphorus ligands covalently attached to a polymeric support which were readily obtained via a solid-phase synthetic protocol.

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