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One-Pot Multistep Synthetic Strategies for the Production of Fenpropimorph Using an Ionic Liquid Solvent

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Abstract:

The one-pot synthesis of the fungicide fenpropimorph has been achieved using two different synthetic strategies in an ionic liquid. The first pathway consists of a Heck coupling followed by reductive amination; the second pathway consists of an aldol condensation followed by hydrogenation/reductive amination. Homogeneous and heterogeneous palladium catalysts have been utilised in the ionic liquid to provide a catalyst/solvent system that is suitable for recycling and process optimisation.

Introduction

Fenpropimorph, 4-[3-(4-*tert*-butylphenyl)-2-methylpropyl]-2,6-dimethylmorpholine (**3**), is a pesticide, specifically categorised as a morpholine fungicide. It finds major use as the active ingredient in agricultural formulations for the control of disease in cereal crops. Industrially, fenpropimorph is produced as the racemic mixture of the cis isomer, although it is known that (*S*)-(−)-enantiomer is known to have the higher fungicidal activity.[1] Currently fenpropimorph, and other similar molecules, is produced in excess of 40 000 tons per annum and is used extensively worldwide. Several patents have been filed concerning the synthesis of fenpropimorph; however, all use multistep, inefficient processes that produce large quantities of waste and yield product that often requires refining.[2−5] For example, the current industrial process uses 3-(4-*tert*-butylphenyl)-2-methylpropenal as the starting material and couples the aldehyde to 1-(2-hydroxypropylamino)-propan-2-ol via a condensation reaction at 165 °C using a solid acid catalyst. The resulting intermediate oxazolidine product is then isolated by distillation before being hydrogenated at 240 °C and 15−25 atm H_2 using a 5%Pd/C catalyst. In this process the overall yield is 52%. When taken with the 50% yield for the initial aldol condensation to form 3-(4-*tert*-butyl-phenyl)-2-methylpropenal, the overall yield from 4-*tert*-butylbenzaldehyde is <30%. Vinković and Šunjić also reported a stereocontrolled synthesis of *cis*-fenpropimorph using a six-step synthesis which affords only 6% overall yield.[6] In addition, two biocatalytic routes to form enantiopure *cis*-fenpropimorph have been reported using a lipase-catalysed acylation of prochiral 2-(4-*tert*-butylbenzyl)-1,3-propanediol and a lipase-catalysed kinetic resolution of racemic 3-(4-*tert*-butylphenyl)-2-methylpropionic acid.[7] The research reported herein demonstrates the possibility of "redesigning" the current synthetic pathway for this material by using an ionic liquid as the solvent of choice to achieve an improved process.

Although ionic liquids have only been studied in detail for organic synthesis/catalytic reactions in the past decade, a wide range of reactions have been demonstrated,[8] and a number of industrial processes have been established, notably by BASF and Degussa.[9] In the case of catalytic processes, the studies in ionic liquids have been dominated by investigations into homogeneous catalyst systems whereby the ionic liquid immobilises the catalyst and allows good separation of the solvent/catalyst system from the products.[8] More recently, the combination of heterogeneous catalysts in ionic liquids has been investigated. In particular, selective hydrogenation,[10,11] selective oxidation,[12] Heck coupling,[13−16] Friedel−Crafts,[17−19] and cyclization reactions[20] have been reported. In virtually all cases the reactions, whether catalytic or stoichiometric, have been single-step processes, and few investigations have been performed whereby the same ionic liquid is used in a number of consecutive reactions.[21] It is unrealistic to envisage a process whereby a number of steps

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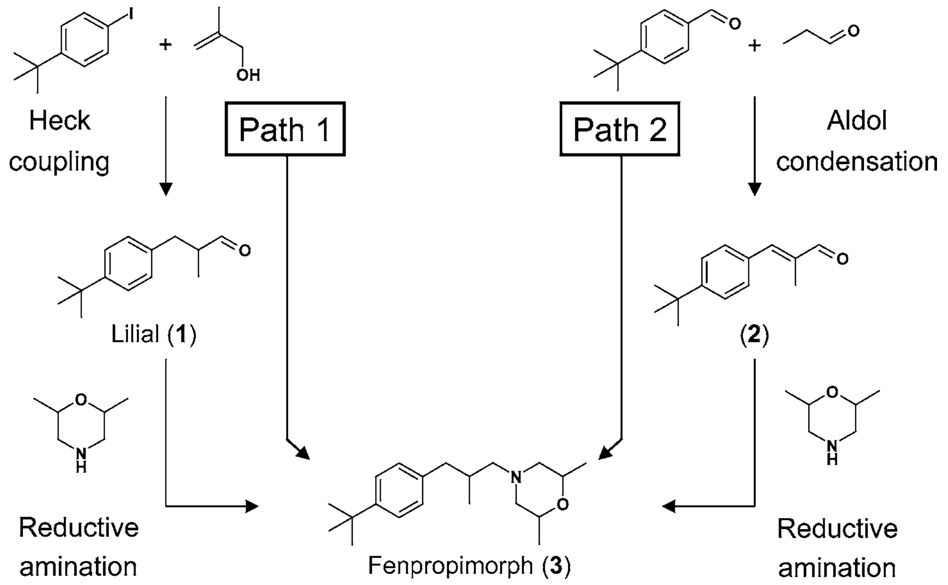
Scheme 1. **One-pot sequential pathways to produce fenpropimorph**



are replaced by ionic liquid processes, particularly where a number of different ionic liquids would have to be used. The major advantage of ionic liquids lies in the changes in rate/selectivity which may be achieved compared to those achieved with organic solvents, with the added economic benefit and the reduction in downstream processing costs. One method to reduce the number of process steps is to combine consecutive steps in the same solvent without intermediate purification, leading to an increase in overall product yield. In this way, the energy costs will be reduced and purification should be simplified.

The two synthetic pathways used for the synthesis of fenpropimorph are shown in Scheme 1. Each pathway contains a carbon−carbon bond-forming reaction via either a Heck coupling (Path 1) or an aldol condensation (Path 2). This is followed by a reductive amination on the aldehyde formed to yield the aminated product. Heck reactions have been studied extensively in ionic liquids using a range of aromatic substrates and olefins.[22,23] In the present study the coupling reagent is an allylic alcohol which has been studied to a much smaller extent than the more reactive allylic esters for example. In particular, the formation of the β-Heck product is required. Ionic liquids have been shown to be versatile in differentiating between the α and β forms; for example, Xaio et al.[24] have recently shown that, by varying the ionic liquid and the phosphine used, the system may be tuned to give almost total selectivity to either isomer. Aldol reactions have also been studied using ionic liquids. For example, both the stereoselective and nonstereoselective aldol condensations have been described,[25] showing increased yields of oligomers $>C_9$ and high enantiomeric excess (ee). In general, the ionic liquid systems show little loss in activity or ee on recycle of the catalyst/ionic liquid system. However, the selectivity with respect to the cross-aldol product compared with that of the self-condensation products has not been addressed.

As part of the preparation for the research performed herein, the specific Heck and aldol condensations leading to Lilial, 3-(4-*tert*-butylphenyl)-2-methylpropanal (**1**), and 3-(4-*tert*-butylphenyl)-2-methylpropenal (**2**), respectively, have been examined recently. The Heck coupling of 2-methyl-prop-2-en-1-ol with 4-*tert*-butyl-iodobenzene was demonstrated to proceed efficiently in ionic liquids, and after extracting with organic and aqueous solvents, recycling of the ionic liquid−homogeneous catalyst system was possible.[16] In the case of the aldol condensation of 4-*tert*-butylbenzaldehyde and propanal, a range of ionic liquids, particularly those based on bis{(trifluoromethyl)sulfonyl}-amide and trifluorotris(perfluoroethyl)phosphate anions, were shown to promote the cross-aldol product over the self-condensation of propanal.[26] Although a range of homogeneously and heterogeneously catalysed hydrogenations have also been performed in ionic liquids, only one report of reductive amination reactions has been reported, using a homogeneous iridium complex in a range of ionic liquids. Compared with organic solvents, the ionic liquid-mediated reactions showed higher selectivities at high conversions.[27]

This paper describes an overall catalytic process used to form fenpropimorph using a single ionic liquid solvent, optimised from the individual reaction steps. The effect of recycling the ionic liquid-catalyst system is examined and the details on how the scaled up process may be operated are presented.

Experimental Section

Unless otherwise stated, all reagents, solvents and catalysts were obtained from Aldrich and used without further purification. 1-Butyl-1-methylpyrolidinium bis{(trifluoro-

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methyl)sulfonyl}amide ([bmpyrr][NTf_2]), 1-butyl-3-methylimidazolium tetrafluoroborate ([C_4mim][BF_4]), and 1-butyl-3-methylimidazolium bis{(trifluoromethyl)sulfonyl}amide ([C_4mim][NTf_2]) were prepared in house using standard literature methods.[28-30] The [NTf_2]$^-$ ionic liquids contained <0.2 wt % water and the [C_4mim][BF_4] 0.66 wt % water as determined by Karl Fischer analysis. For the [NTf_2]$^-$ ionic liquids, the residual halide content was <7.2 ppm, and for [C_4mim][BF_4] the residual chloride content was <7.1 ppm as determined by ion chromatography.[31] The heterogeneous palladium catalysts 5 wt % Pd/C (BET surface area 652 m^2 g^{-1}; metal dispersion 10%) and 5 wt % Pd/Al_2O_3 324 (BET surface area 134 m^2 g^{-1}; metal dispersion 14%) were supplied by Johnson Matthey. $PdCl_2$ was supplied by Fluka and used as received. The gases used were all research grade and were supplied by BOC.

^{1}H NMR spectra were recorded on a Bruker Advance DRX 500 MHz NMR spectrometer. GC-FID samples were analysed using a Hewlett-Packard 6890 GC fitted with an RTX-5 column (30 m, 0.25 μm diameter). The retention times of the peaks were compared against those of authentic samples. GC−MS (Perkin-Elmer Turbo Mass) was performed using a PE5MS column (length, 30 m; thickness, 0.25 μm; IDO, 0.32 mm). The conversions were adjusted using calculated sensitivity factors for starting materials and products.

Three reactors were used for screening, small-scale kinetic studies, and scale-up investigations. The screening experiments were carried out in a Baskerville mini-autoclave with magnetic stirring, denoted as the Baskerville reactor throughout the text. The small-scale kinetics were performed in a Hazards Evaluation Laboratory 50 cm^3 autoclave equipped with a gasifying overhead impeller and four baffles, denoted as the HEL reactor throughout the text. Scaled up reactions were performed using a 300 cm^3 Parr stainless steel autoclave with a gasifying overhead impeller and four baffles, denoted as the Parr reactor throughout the text.

Reductive Amination Procedure. Typically, ionic liquid or organic solvent (2 cm^3), catalyst (27 mg), equimolar substrate, and amine (2.5 mmol; substrate/catalyst $\approx$ 100) were introduced to the autoclave and purged with nitrogen. The reactor was pressurised with hydrogen and heated. Once the set temperature had been reached, the stirring was started and left for the desired time, after which the stirring was stopped and the pressure released. Samples were taken periodically during the reaction whilst still under pressure. The ionic liquid samples were extracted with cyclohexane in a volume ratio 1:5 (IL/cyclohexane) and filtered before analysis by GC-FID and GC−MS.

Procedure for the One-Pot Heck-Reductive Amination Reaction: Path 1. To a glass tube were added 4-*tert*-butyliodobenzene (10 mmol), 2-methylprop-2-en-1-ol (12 mmol), triethylamine (12 mmol), $PdCl_2$ dissolved in 3 cm^3 [bmpyrr]-[NTf_2] (0.05 mmol equivalent of palladium). The tube was then loaded into the Baskerville reactor, and the reaction mixture was stirred at 100 °C for 4 h under nitrogen to ensure complete conversion of 4-*tert*-butyl-iodobenzene. The reaction was cooled to room temperature, 2,6-dimethylmorpholine added, and the reaction mixture pressurised to 10 atm hydrogen atmosphere. The reductive amination reaction was performed at room temperature for 16 h. The reaction was analysed following both the initial Heck coupling and the reductive amination reaction.

Procedure for One-Pot Aldol-Reductive Amination Reaction: Path 2. The Parr reactor was charged with [bmpyrr][NTf_2] (30 cm^3), 4-*tert*-butylbenzaldehyde (400 mmol), 2,6-dimethylmorpholine (240 mmol), and 5 wt % Pd/Al_2O_3 (8.5 g, 4 mmol equivalent of palladium). The reaction mixture was stirred at 600 rpm whilst propanal (400 mmol) was pumped into the reactor over 4 h using a peristaltic pump. The reaction was allowed to stir until GC analysis sample showed complete conversion, typically after 12 h. A further quantity of 2,6-dimethylmorpoline (160 mmol) was added. Then the vessel was sealed, purged with nitrogen, and pressurised with 10 atm hydrogen. The reactor was stirred at 600 rpm at 60 °C for 20 h. The reaction was analysed following both the initial aldol condensation and the reductive amination reaction.

Recycle Procedure. For both the reductive amination reactions and the one-pot syntheses using Path 2, the product was removed from the ionic liquid−catalyst mixture by decantation. Any catalyst entrained in the product layer was filtered off and returned into the ionic liquid layer before the reaction was restarted to maintain the catalyst loading. This was typically <5% of the original catalyst mass. Fresh starting materials were added to the catalyst and ionic liquid reaction mixture and the initial reaction procedure was repeated.

Results

Reductive Amination. Table 1 summarises the reductive amination of different aldehydes by different bases using 10% Pd/C, 5% Pd/Al_2O_3, and $PdCl_2$ in the Baskerville mini-autoclave performed in [bmpyrr][NTf_2] over 16 h. Clearly both homogeneous and heterogeneous catalysts result in high yields of reductive amination products for a range of aldehyde-secondary amine combinations in both ionic liquids and conventional solvents. However, following reaction with $PdCl_2$ in ethanol and [bmpyrr][NTf_2] a significant formation of palladium black was observed. Although this was not unexpected in the case of molecular solvents, it may be surprising that the ionic liquid solvent did not stabilise the cationic palladium in solution. This may be due to the decomposition of the palladium chloride on dissolution in the ionic liquid to form palladium nanoparticles which aggregate under hydrogen. Nanoparticle formation has been observed on dissolution of palladium salts by EXAFS and TEM studies previously in ionic liquids.[32] In these cases, the ionic liquid stabilised small Pd nanoparticles (<2 nm),

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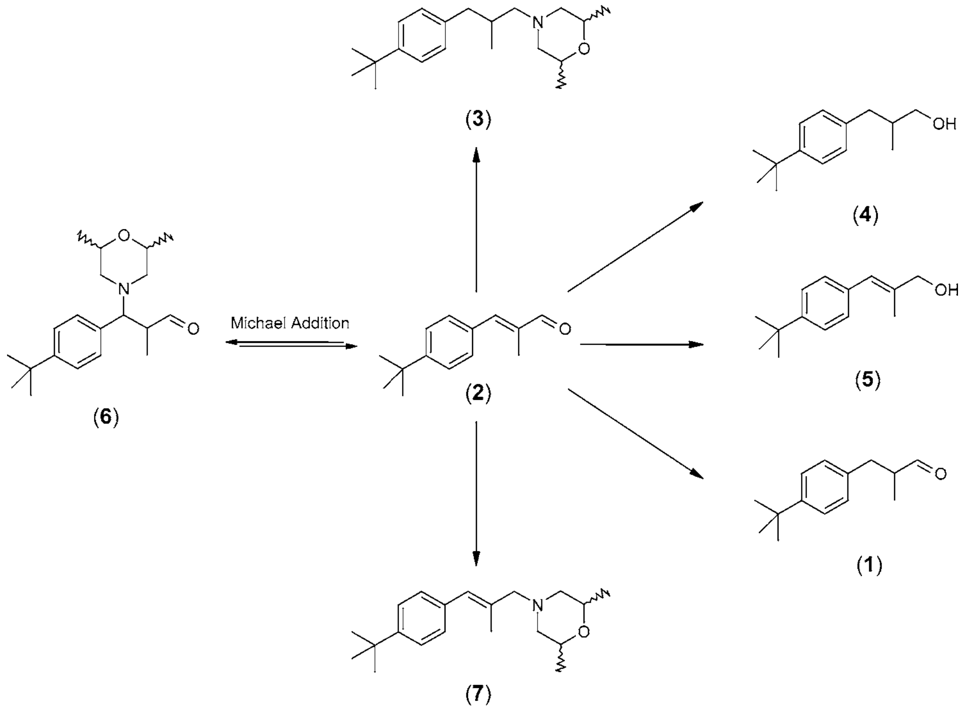
Table 1. **Percentage conversion with respect to the aldehyde and isolated yield of saturated reductive amination product following the reaction of a range of aldehydes with secondary amines[a] using $PdCl_2$, 5%Pd/C, and 5%Pd/Al_2O_3 (100:1; aldehyde:Pd) in ethanol and $[bmpyrr][NTf_2]$ at 60 °C and 10 atm hydrogen for 16 h in the Baskerville reactor**

aldehyde	amine	catalyst, solvent	% conversion	% yield	*cis*/*trans*
1	**A**	$PdCl_2$, EtOH	92	92	62/27
1	**A**	$PdCl_2$, $[bmpyrr][NTf_2]$	92	92	62/27
1	**A**	Pd/C, EtOH	99	82	73/27
1	**A**	Pd/C, $[bmpyrr][NTf_2]$	99	88	73/27
1	**A**	Pd/Al_2O_3, $[bmpyrr][NTf_2]$	99	99	71/29
1	**B**	Pd/Al_2O_3, $[bmpyrr][NTf_2]$	99	99	
1	**C**	Pd/Al_2O_3, $[bmpyrr][NTf_2]$	99	99	
2	none	Pd/C, $[bmpyrr][NTf_2]$	60	58[c]	
2	**A**	Pd/C, $[bmpyrr][NTf_2]$	85	83	75/8
2	Et_3N	Pd/C, $[bmpyrr][NTf_2]$	76	75[c]	
2	$(i\text{Pr})_2EtN$	Pd/C, $[bmpyrr][NTf_2]$	97	93[c]	
2	**A**	Pd/C, Toluene	93	93	68/25
2	**B**	Pd/C, $[bmpyrr][NTf_2]$[b]	80	33[d]	
2	**C**	Pd/C, $[bmpyrr][NTf_2]$[b]	71	51[d]	
8	**A**	Pd/C, $[bmpyrr][NTf_2]$	83	83	54/29
9	**A**	Pd/C, $[bmpyrr][NTf_2]$	100	99	58/41

[a] **1** = Lilial; **2** = 3-(4-*tert*-butylphenyl)-2-methylpropenal; **8** = 4-*tert*-butylbenzaldehyde; **9** = 2-methyl-2-pentanal; **A** = 2,6-dimethylmorpholine; **B** = piperidine; **C** = morpholine. [b] Reaction temperature was 90 °C, at 60 °C the conversions were ~10% after 16 h. [c] Formation of Lilial. [d] Balance Lilial.

Scheme 2. **Reaction products originating from the reductive amination of 3-(4-*tert*-butylphenyl)-2-methylpropenal and 2,6-dimethylmorpholine**



and a precipitate was not observed. The aggregation is not associated with the reductive amination reaction as palladium black is formed when $PdCl_2$ dissolved in $[bmpyrr][NTf_2]$ is exposed to 10 atm H_2 in the absence of either substrate.

As expected, for the reductive amination of Lilial (**1**) and 4-*tert*-butylbenzaldehyde with 2,6-dimethylmorpholine only fenpropimorph (**3**) and 4-(4-*tert*-butylphenyl)-2,6-dimethylmorpholine, respectively, are formed. In the case of 2-methyl-2-pentenal and 3-(4-*tert*-butylphenyl)-2-methylpropenal (**2**), a number of products are possible, as illustrated in Scheme 2 for the case of **2**. For both α,β-unsaturated aldehydes, high selectivity to the saturated reductive amination products were observed with <1% of any other product. This is important in the case of formation of fenpropimorph from the aldol condensation derived unsaturated intermediate, **2**, as, whilst it is possible to reduce **2** to Lilial highly selectively (>98%) using 10% Pd/C in $[bmpyrr][NTf_2]$ in the absence of base followed by reductive amination, this is not required, and a one-step process can be used. In addition to the products shown in Scheme 2, isomers containing the *cis*- and *trans*-2,6-dimethylmorpholinium species are present. The starting

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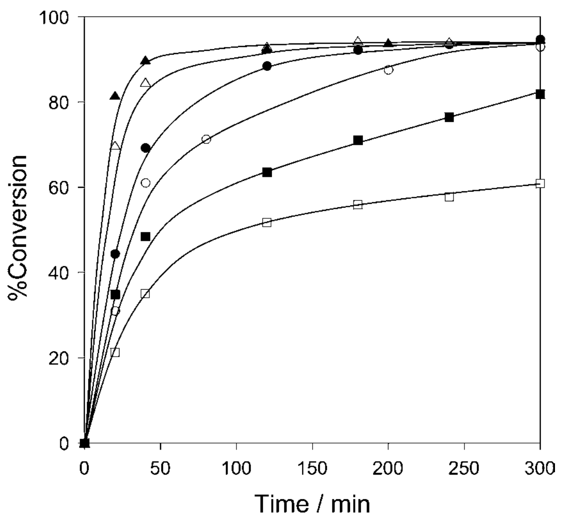

Figure 1. **Percentage conversion to fenpropimorph as a function of time during the reaction of 3-(4-*tert*-butylphenyl)-2-methylpropenal (2) with 2,6-dimethylmorpholine using 5% Pd/Al_2O_3 (aldehyde/Pd, 250:1) in a toluene (△), fenpropimorph (▲) water (□), [C_4mim][NTf_2] (●), [C_4mim][BF_4] (■), and [bmpyrr][NTf_2] (○) at 60 °C and 10 atm hydrogen in the HEL reactor.**

material contains the *cis* and *trans* forms in a 7:3 ratio which is maintained at 100% conversion; however, as shown in Table 1, at intermediate conversions the ratio is decreased, showing the higher rate of reaction for *trans*-2,6-dimethylmorpholine compared with that for *cis*-2,6-dimethylmorpholine. Interestingly, the rate of reaction for the reductive amination is much higher compared with the hydrogenation of the α,β-unsaturated aldehyde in the absence of amine. This is due to the presence of the base and not due to the mechanism of the reductive amination reaction as a similar rate increase is also seen if a tertiary amine is substituted for the secondary amine. In the presence of diisopropylethylamine (Hunig's base), **2** is reduced to Lilial as expected since Hunig's base is a tertiary amine and therefore cannot form the reductive amination product. Although this may be associated with the amine modifying the surface of the catalyst, this is unlikely in the case of Hunig's base which is generally considered as uncoordinating due to the steric bulk of the branched alkyl chains. Reaction rate changes have been observed previously for hydrogenation reactions in the presence of N-containing bases; however, both decreased as well as increased rates have been reported.[33]

Although similar selectivities are observed in both ionic liquids and molecular organic solvents, as found with other hydrogenations using heterogeneous catalysts in ionic liquids, a significant decrease in the activity of the catalyst was observed compared with that in molecular solvents (Figure 1 and Table 2).[10] This decrease may be understood by comparing the viscosity of the ionic liquid and the hydrogen gas solubility in ionic liquids compared with those in molecular solvents. The increased viscosity of the ionic liquids decreases the mass transport in the solvent which is exacerbated in the presence of a heterogeneous catalyst where the solvent/substrate must penetrate the pores of the catalyst.

Table 2. **Percentage product distribution and conversion of 3-(4-*tert*-butylphenyl)-2-methylpropenal after the reductive amination with 2,6-dimethylmorpholine using 5% Pd/Al_2O_3 (250:1 aldehyde/Pd) in a range of solvents at 60 °C and 10 atm hydrogen for 5 h in the HEL reactor**

	% product distribution[a]				
solvent	**1**	**4**	**5**	**3**	%conversion
toluene	0	6	0	94	100
water	23	7	7	61	98
fenpropimorph	0	0	5	95	100
[bmpyrr][NTf_2]	5	0	2	93	100
[C_4mim][NTf_2]	1	0	4	95	100
[C_4mim][BF_4]	12	1	3	82	98

[a] **1** = Lilial; **3** = fenpropimorph; **4** = 3-(4-*tert*-butylphenyl)-2-methylpropanol; **5** = 3-(4-*tert*-butylphenyl)-2-methyl-propenol.

Table 3. **Percentage conversion after the Heck coupling[a] of 4-*tert*-butyliodobenzene with 2-methyl-prop-2-en-1-ol and percentage yield of fenpropimorph following the reductive amination[a] reaction with 2,6-dimethylmorpholine during the one-pot sequential reaction (Path 1) using $PdCl_2$ and 5% Pd/C in a range of solvents**

catalyst	solvent	Heck % conversion	% yield fenpropimorph
Pd/C	[bmpyrr][NTf_2]	99	65
Pd/C	[$N(C_4H_9)_4$]Br	80	51
Pd/C	No Solvent	40	14
Pd/C	*N*-methylpyrrolidinone	99	72
$PdCl_2$	[bmpyrr][NTf_2]	99	81

[a] The Heck coupling was performed at 100 °C for 4 h, and the reductive amination was performed at room temperature for 16 h under 10 atm hydrogen in a Baskerville reactor.

In addition, hydrogen has a lower solubility in ionic liquids compared with that in many organic solvents; this results in a reduction of the effective pressure of the system and lowers the reaction rate accordingly. It is interesting to note that in homogeneously catalysed hydrogenations such an effect is not observed, and similar reaction rates are found in molecular and ionic solvents.[34]

One-Pot Synthesis to Fenpropimorph: Path 1. The combined Heck reaction−reductive amination one-pot synthesis, i.e. performing the Heck reaction in the presence of amine and hydrogen atmosphere, was not possible in either molecular solvents or ionic liquids due to the rapid hydrodehalogenation of 4-*tert*-butyliodobenzene to *tert*-butylbenzene. Using 5% Pd/C, no reductive amination or Heck coupling products obtained. Similarly, using $PdCl_2$ dehalogenation also occurred, but due to the slower rate of this reaction compared with the Heck process, 15% conversion to Lilial was achieved; however, again no reductive amination products were observed.

Table 3 summarises the yield of fenpropimorph resulting from the sequential one-pot synthesis, i.e. the Heck coupling of 4-*tert*-butyliodobenzene with 2-methyl-prop-2-en-1-ol followed by the reductive amination using 2,6-dimethylmorpholine in a range of solvents. For each reaction mixture,

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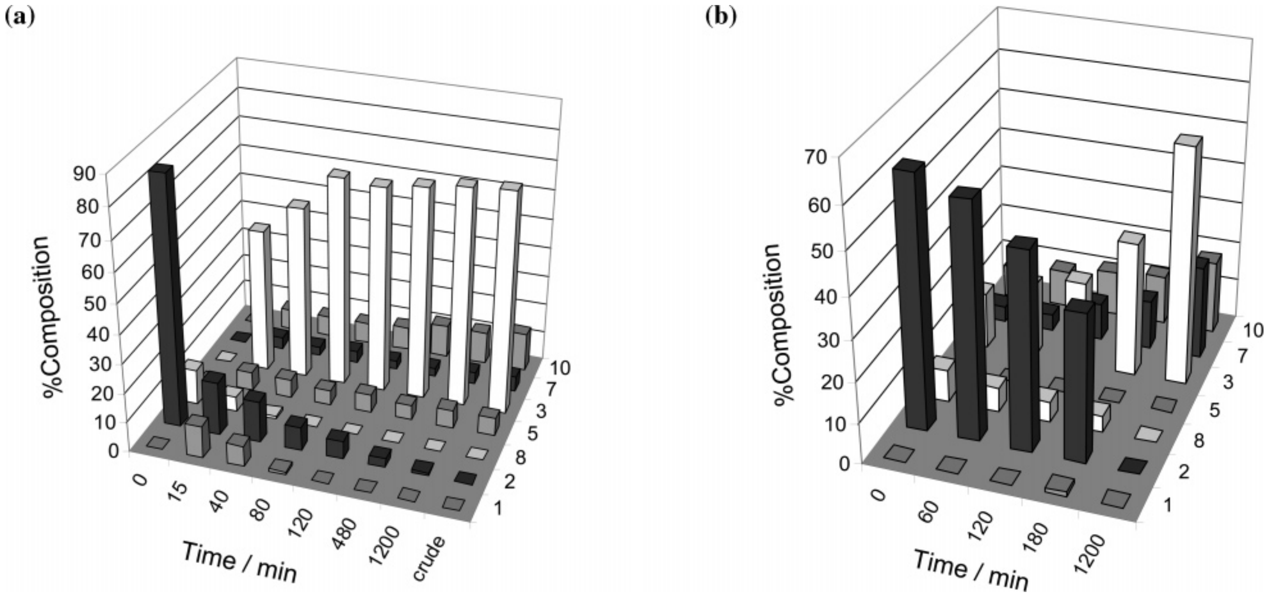

Figure 2. **Percentage composition as a function of time of the reductive amination with 2,6-dimethylmorpholine using 5% Pd/Al_2O_3 (100:1 aldehyde/Pd) in [bmpyrr][NTf_2] at 60 °C and 10 atm hydrogen in the Parr reactor following the aldol condensation of 4-*tert*-butylbenzaldehyde and propanal during (a) the first one-pot sequential reaction (Path 1) and (b) on the second recycle. 1 = Lilial; 2 = 3-(4-*tert*-butylphenyl)-2-methylpropenal,; 3 = fenpropimorph; 5 = 3-(4-*tert*-butylphenyl)-2-methyl-propenol; 7 = 3-[4-(2,6-dimethylmorpholino)]-2-methyl-1-(4-*tert*-butylphenyl)-1-propene; 8 = 4-*tert*-butylbenzaldehyde; 10 = 4-(4-*tert*-butylphenyl)-2,6-dimethylmorpholine. The Michael adduct has been removed in each case for clarity.**

the reductive amination was performed on the reaction mixture from the Heck reaction without isolation of the Lilial Heck product from the solvent system. With the exception of the solventless media, good yields of fenpropimorph were found for both ionic liquids and molecular solvent systems. For the solventless system, the mixture became highly viscous following the Heck reaction due to the formation of triethylammonium iodide which reduced the mass transport in the reductive amination.

Although it was possible to perform the one-pot synthesis using Path 1, this system was not recyclable. As described above, the reductive amination using the homogeneous catalysts formed palladium black which was unreactive for the Heck reaction on subsequent reactions. This problem should be alleviated using the heterogeneous catalyst; however, during the Heck reaction the palladium is leached from the support to form colloidal palladium in solution which then precipitates from solution during the reductive amination.[16]

One-Pot Synthesis to Fenpropimorph: Path 2. In Path 2, the propanal is added slowly during the aldol condensation in the presence of 60 mol % 2,6-dimethylmorpholine as the base. Following the aldol condensation, a further 40 mol % of 2,6-dimethylmorpholine is added for the reductive amination; i.e. the catalyst in the first reaction is used as one of the reactants in the second stage. Figure 2a shows the result of the reductive amination following the aldol condensation of 4-*tert*-butylbenzaldehyde with propanal using 2,6-dimethylmorpholine as the base in the presence of 5% Pd/Al_2O_3. The aldol condensation was stopped after the addition of 100 mol % propanal so as to minimise the formation of the self-aldol condensation product of propanal, 2-methyl-2-pentenal. As found for the sequential reaction from Path 1, high conversion to fenpropimorph was observed after 20 h with an overall yield for the aldol and reductive amination reactions of 75%. Understandably, the major by-product was 4-[(4-*tert*-butylphenyl)]-2,6-dimethylmorpholine from the reductive amination of unreacted 4-*tert*-butylbenzaldehyde. However, unlike in the reductive amination of the isolated **2**, the one-pot reaction also formed 3-(4-*tert*-butylphenyl)-2-methyl-propenol (**5**) and 3-[4-(2,6-dimethylmorpholino)]-2-methyl-1-(4-*tert*-butylphenyl)-1-propene (**7**), albeit with yields of only 6% and 5%, respectively.

The selectivity and rate of the aldol condensation reaction was not substantially affected by the presence of the heterogeneous catalyst. However, in addition to the formation of the cross- and self-aldol products, small amounts (~6%) of the Michael addition product 3-(4-*tert*-butylphenyl)-3-(2,6-dimethylmorpholin-4-yl)-2-methyl-propanal (**6**) was found (Scheme 2); this was not observed in the absence of the catalyst using a small-scale reaction.[26] This may be associated with the more efficient stirring in the larger-scale experiments compared with the magnetically stirred reactions reported previously.[26] Aza-Michael additions, i.e. Michael additions that are carried out with amine nucleophiles, are known to be promoted by water.[35] In the ionic liquid it has been demonstrated that a solid is formed when the 2,6-dimethyl morpholine is mixed with 4-*tert*-butylbenzaldehyde; this precipitate is thought to be the iminium salt. On the small scale, the reaction medium is poorly mixed, and therefore, the water formed during the aldol reaction cannot effectively promote the Michael addition reaction. In contrast, using an overhead mechanical stirrer enables the solid to be broken up more efficiently, releasing water as the reaction progresses, thereby magnifying the effect of water. No Michael addition

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(35) Naidu, B. N.; Li, W. Y.; Sorenson, M. E.; Connolly, T. P.; Wichtowski, J. A.; Zhang, Y. H.; Kim, O. K.; Matiskella, J. D.; Lam, K. S.; Bronson, J. J.; Ueda, Y. *Tetrahedron Lett.* **2004**, *45*, 1059.

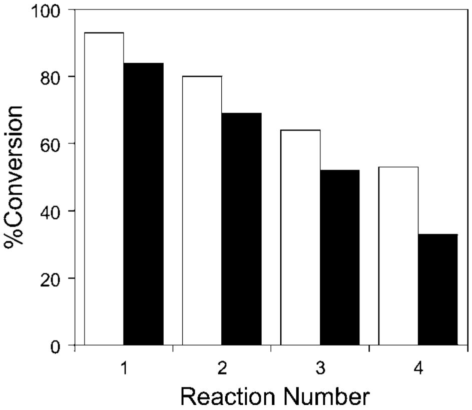

Figure 3. **Variation of the percentage conversion to fenpropimorph as a function of recycle following the reaction of 3-(4-*tert*-butylphenyl)-2-methylpropenal (2) with 2,6-dimethylmorpholine using 5% Pd/Al_2O_3 (250:1 aldehyde/Pd) in [bmpyrr][NTf_2] at 60 °C and 10 atm hydrogen in the HEL reactor where the aldehyde used is formed ex situ (☐) and in situ (■), i.e. the reduction is performed as part of the sequential one-pot process in Path 2.**

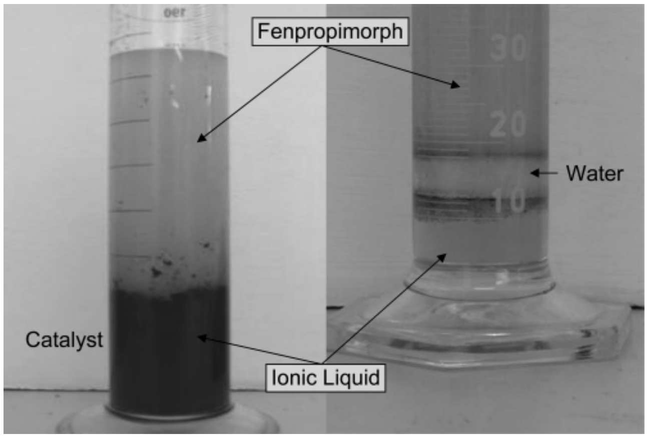

Figure 4. **Images of the reaction mixture following the one-pot sequential reaction (Path 2) using 5% Pd/Al_2O_3 in [bmpyrr][NTf_2] in the Parr reactor (a) directly following reaction and (b) after catalyst removal.**

product is observed after the reductive amination as this reaction is reversible, and therefore, the Michael adducts break down as the reductive amination proceeds and leading to the formation of the desired product only. Although aza-Michael addition reactions have also been shown to be promoted by palladium and other transition metals,[36] it is not thought that the presence of the catalyst contributes to the reaction as similar yields are observed in the absence of catalyst using an overhead stirrer.

Figures 2b and 3 show the effect of recycling the catalyst−ionic liquid system in the Parr and HEL reactors, respectively. Following the initial aldol-reductive amination reactions, the fenpropimorph formed was decanted from the ionic liquid solvent. This was subsequently recharged with 4-*tert*-butylbenzaldehyde and the aldol condensation repeated followed by the reductive amination. Clearly, a significant reduction in the reaction rate and an increase in the number of by-products is observed, as shown for the second recycle data in the Parr reactor in Figure 2b. This does not reflect a significant change in the selectivity/conversion achieved in the aldol condensation as, with the exception of a small increase in the Michael addition product, no changes in the conversion versus selectivity profile compared with the initial aldol reaction were found on recycle.

A reduction in rate is also observed on recycling the catalyst−ionic liquid system for the reductive amination reaction of isolated **2** using 2,6-dimethylmorpholine after 6 h (Figure 3). With an increasing number of reactions, the conversion is found to drop gradually. Although a similar deactivation was reported by Anderson et al. for the selective hydrogenation of α,β-unsaturated aldehydes, in that case the decrease was a step change, and following the first reaction the rate remained constant for subsequent reactions.[10] In this case, the sharp decrease was attributed to pore blocking of the catalyst, and the activity could not be recovered by washing the catalyst or catalyst−ionic liquid system. Although a drop in the catalyst BET surface area was observed following the reaction in the present case, on washing the catalyst with acetonitrile, the original surface area was recovered. Furthermore, after washing the catalyst followed by drying, redispersion in fresh ionic liquid resulted in >95% of the activity found on the next reaction.

The reduction in rate on recycle cannot be explained by palladium leaching during either the aldol or reductive amination reactions. The average dissolved palladium content was found to be less than 3 ppm by ICP from either palladium supported on carbon or alumina in either the fenpropimorph layer or in the ionic liquid after separation of the catalyst.

Due to the method workup, i.e. simple decantation of the fenpropimorph layer from the ionic liquid, the solubility of the product in the [bmpyrr][NTf_2] was measured and found to be ~0.144 M. The low level of solubility of fenpropimorph in the ionic liquid allows for simple product recovery through layer separation. The presence of low concentrations of the product in the ionic liquid may be the source of the change in rate and selectivity on recycle; however, the reductive amination of **2** performed in fenpropimorph as the solvent resulted in similar activity as found in the ionic liquid (Figure 1). Similarly, the other hydrocarbon by-products, in particular 4-(4-*tert*-butylphenyl)-2,6-dimethylmorpholine which is the least efficiently extracted by-product of fenpropimorph, are not thought to be responsible for the changes observed on recycle. It should be noted that polymeric material may also be formed in the aldol condensation from multiple additions and may be adsorbed strongly on the catalyst or be retained in the ionic liquid. However, reuse of either the catalyst with fresh ionic liquid or the ionic liquid with fresh catalyst showed no change in the rate of the reductive amination of isolated **2** compared with the reaction performed with unused catalyst and ionic liquid.

Following separation of the catalyst from the reaction mixture, unexpectedly three phases of liquid were observed, shown in Figure 4. Using a hydrophobic ionic liquid, the water formed in both the aldol condensation and the reductive amination reactions separates from the ionic liquid and

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[36] Kawatsura, M.; Hartwig, J. F. *Organometallics* **2001**, *20*, 1960.

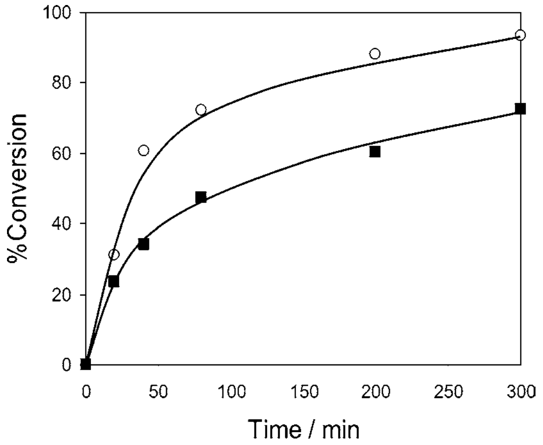

Figure 5. **Variation of the percentage conversion to fenpropimorph following the reaction of 3-(4-*tert*-butylphenyl)-2-methylpropenal with 2,6-dimethylmorpholine using 5% Pd/Al_2O_3 (250:1 aldehyde/Pd) in [bmpyrr][NTf_2] at 60 °C and 10 atm hydrogen in the HEL reactor with (■) and without 3 mol equiv (○) of water with respect to the 3-(4-*tert*-butyl-phenyl)-2-methylpropenal (2).**

product phases. Commonly, the solvent makes up the majority of the volume in the reaction, and thus, even if a hydrophobic solvent is used, any water remains in the solvent. In the present case, the ionic liquid is only required to ensure that the aldol condensation has high selectivity and to support the catalyst for the reductive amination; in both cases, only a minimum volume is required. In these reactions, the volume ratio between the water formed if 100% reaction and the ionic liquid used is 1:2 (H_2O/IL). Figure 5 shows the effect of water on the reductive amination of unsaturated Lilial using 5% Pd/Al_2O_3 in [bmpyrr][NTf_2]. Using 3 mol equiv of water to the amount of substrate, i.e. the quantity of water formed during two aldol condensations plus a reductive amination reaction, to represent the effect of a recycle reaction, a 44% reduction in the initial rate of reaction is observed. Similarly when water is used as the solvent, a significant reduction in the rate is found compared with use of the ionic liquids and toluene. Interestingly, in water, the yield of 3-(4-*tert*-butylphenyl)-2-methyl-propenol is substantially greater than in ionic liquids or toluene, even when the [bmpyrr][NTf_2] was spiked with water, as shown in Table 2 and Figure 1. The fact that in the one-pot reaction so little 3-(4-*tert*-butyl-phenyl)-2-methyl-propenol is formed indicates that the reaction still proceeds in the ionic liquid phase. The reduction in reaction rate found in the hydrophobic ionic liquid in the presence of water may, therefore, be due to the water extracting the amine from the ionic liquid phase and consequently reducing its concentration resulting in a decrease in the overall reaction rate. This possibility has been verified by measuring the partition coefficient between water and [bmpyrr][NTf_2] for 2,6-dimethylmorpholine, which has a value for $[\text{amine}]_{IL}/[\text{amine}]_{H2O}$ of 0.31. In addition, when the catalyst/ionic liquid layer was dried between recycles, conversions are significantly improved when compared with the nondried system. For example, after three reactions in the HEL reactor, the conversion for the dried system was >10% higher than that found for the nondried system.

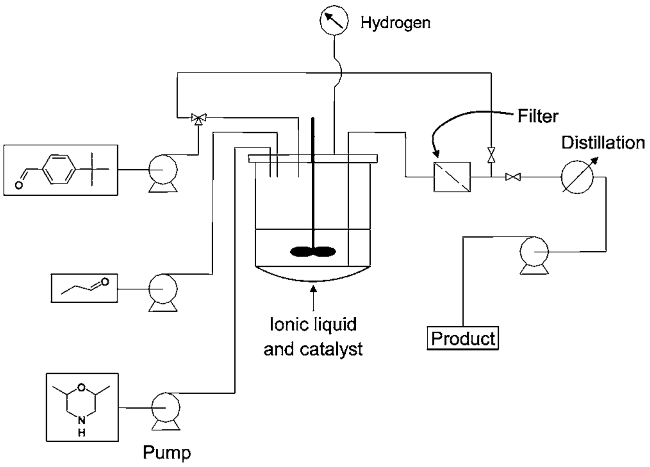

Figure 6. **Schematic process diagram for the scale-up of Path 2. Aldehyde and amine are charged into the reactor containing ionic liquid and catalyst while the second aldehyde is pumped in slowly with stirring until complete conversion. Further amine is introduced, hydrogen pressure is applied with heating and stirring to completion. The reaction mixture is then allowed to settle, the product layer is pumped off for filtration and distillation. The process steps may then be repeated.**

A combined aldol reaction—reductive amination one-pot synthesis was also performed, i.e. pumping the propanal into the reactor under 2.5 atm of hydrogen at room temperature in the presence of 100 mol % 2,6-dimethylmorpholine; after the addition the vessel was pressurised to 10 atm. In this case, the reaction mixture became highly viscous; however, a yield of 36% fenpropimoph was found after solvent extraction using cyclohexane. In addition to fenpropimorph a large number of by-products were also observed. As with the combined reaction in Path 1, although the single process step reaction is possible, there are significant disadvantages of performing the combined reaction over the sequential one-pot process.

Comparison of Process Paths. It is clear that although both pathways are viable, Path 2 offers a more atom-efficient process as well as the possibility of recycling the catalyst/ionic liquid system. The major disadvantages of Path 2 are the increased number of by-products and a small decrease in overall yield of fenpropimorph compared with those of Path 1. The atom efficiency for Path 1 was calculated to be 46% whilst that from Path 2 was 67%. In addition, the *E*-factors were found to be 1.26 and 0.37 for Paths 1 and 2, respectively.[37] The high efficiency of Path 2 is due, in part, to the use of one of the reagents as a catalyst in a previous step but also that the main by-product is water. Path 1 is inefficient because of its triethylammonium iodide salt by-product formation. Furthermore, the reaction profile and rates could be correlated on scales ranging from 10 to 150 cm^3 in Path 2. Figure 6 shows the proposed process diagram for the scaled-up overall process where after reaction the product is isolated by distillation and the ionic liquid/catalyst system is dried in situ and recycled.

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(37) The *E*-factor = total waste (kg)/product (kg). The *E*-factors were calculated without taking into account the water as waste and assuming 100% recovery of the ionic liquid and catalyst. Sheldon, R. A. *J. Mol. Catal. A: Chem.* **1996**, *107*, 75.

Conclusions

Two routes to fenpropimorph have been demonstrated via a Heck reaction or an aldol condensation and then a reductive amination reaction. Although both Heck and aldol processes proceed efficiently in the ionic liquid, only the aldol pathway may be recycled. By using the amine catalyst from the aldol condensation as the reagent in the subsequent reductive amination reaction, a highly atom-efficient process is possible. A versatile multistep catalytic synthesis using a single ionic liquid is possible with the ionic liquid able to be easily recycled, albeit with a drop in conversion and a decrease in the selectivity. In contrast, using conventional molecular solvents, the separation is more difficult and requires evaporation and recondensation of the solvent.

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