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A monolith immobilised iridium Cp* catalyst for hydrogen transfer reactions under flow conditions

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An immobilised iridium hydrogen transfer catalyst has been developed for use in flow based processing by incorporation of a ligand into a porous polymeric monolithic flow reactor. The monolithic construct has been used for several redox reductions demonstrating excellent recyclability, good turnover numbers and high chemical stability giving negligible metal leaching over extended periods of use.

Introduction

Transition metal mediated hydrogen transfer reactions are normally characterised by relatively mild conditions enabling the reduction of aldehydes, ketones and imines or the corresponding oxidation of alcohols and amines in high yields.[1] In these processes the catalyst typically acts as a hydride relay mediating transfer between two starting materials in different oxidation states (*i.e.* alcohol/aldehyde) operated under pseudo-equilibrium type conditions.[2] Consequently, the processes are often described as "hydrogen transfer" or "borrowing hydrogen" reflecting the overall redox-neutral transformation.

Although the use of homogeneous metal catalysts have shown significant scope allowing hydrogen transfer reactions to be scaled to kilogram levels,[3] the issue of catalyst separation from the product, and thereby achieving acceptable ppm contamination levels is still a major challenge. In addition many of the most effective catalysts are based upon precious transition metals such as Pt, Ru, Ir and Rh that, without an effective recycling strategy, preclude their use in industrial important processes. An obvious solution is to therefore carry out immobilisation of the catalyst onto a solid support facilitating post reaction purification by filtration or engineering fixed bed catalyst reactor systems. Consequently several immobilisation strategies for this class of catalyst have previously been investigated.[4] However, in these cases high metal leaching or significant catalyst deactivation compared to the non-immobilised species has been observed. To overcome some of these issues we herein describe an alternative immobilisation strategy designed specifically for use in flow based processing scenarios. We made use of the known iridium complex **1**[5] which seemed highly amenable to simple ligand modification

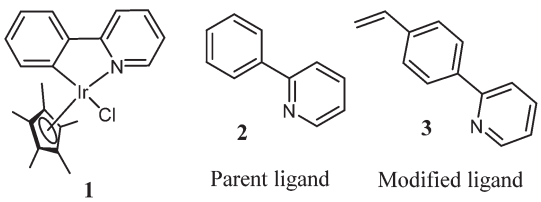

Fig. 1 Parent iridium Cp* type catalyst **1**, the parent ligand **2** and the polymerisable ligand derivative **3**.

(**2** → **3**) for rapid incorporation into a polymeric matrix (Fig. 1). Interestingly, complex **1** had shown reasonable activity under photoirradiation for the catalytic oxidation of water indicating a robust complex, stable ligand association and proven potential for redox cycling.[6]

Results and discussion

Our target was to prepare a monolith based reactor to act as both the catalyst support and a direct plug in flow cartridge.[7,8] Monoliths are a single continuous piece of permeable media constructed from either organic or inorganic materials. In the context of this work, the monolith was generated *via* suspension polymerisation to create a permanent, well-defined porous architecture that retained its structural integrity independently of the solvent or reagents used due to a high degree of crosslinking within the polymer matrix. This type of construct is also known to offer significantly higher mass transfer compared to traditional bead immobilisation formats as it relies on convective flow instead of diffusion.[7] Furthermore, large pressure drops are not usually observed using such monoliths in flow processes,[9] this is desirable to ensure the consistency of the flow process over time.

Our plan was therefore to generate the monomer ligand **3**, polymerise it into a monolith and then finally load the iridium metal. The functional monomer ligand **3** was easily prepared

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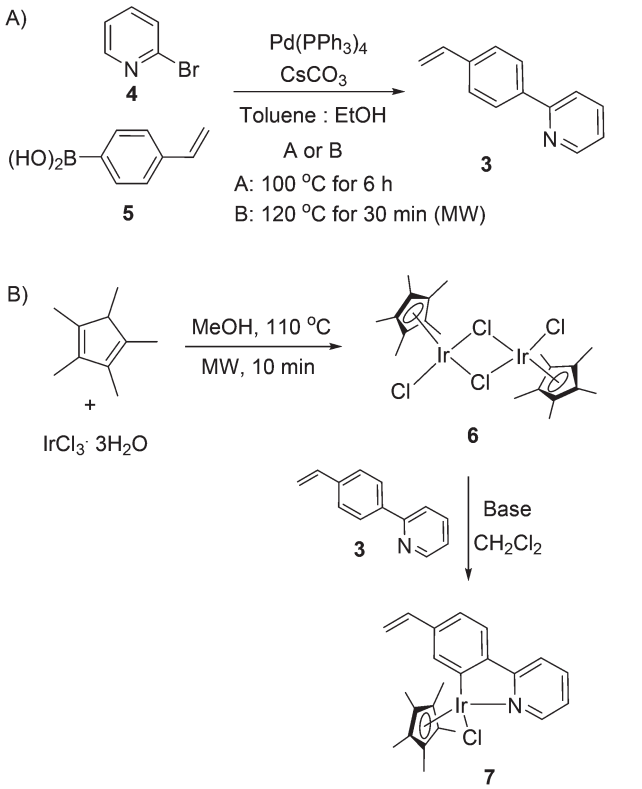


Scheme 1 Synthesis of the functional monomer **3** (A) and preparation of complex **7** (B).

from commercially available starting materials; 2-bromopyridine (**4**) and 4-vinylphenylboronic acid (**5**) were reacted *via* a palladium catalysed cross coupling reaction reproducibly in >82% yield on a 5–10 mmol scale (Scheme 1).[10] With easy access to gram quantities of the monomer we first evaluated its coordination and stability in association with the iridium metal generating complex **7**.

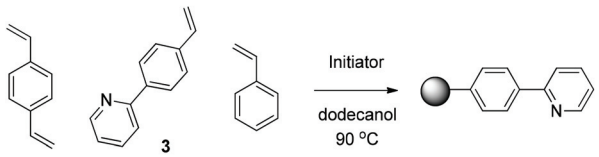
The original complex **1** is synthesised by ligand exchange of the dimeric complex pentamethylcyclopentadienyliridium(III) chloride (**6**, CAS number 12354-84-6) with 2-phenylpyridine. Although precursor **6** is commercially available, it is extremely expensive. We alternatively found it convenient to prepare the iridium dimer **6** by simply heating iridium(III) chloride hydrate and pentamethylcyclopentadiene in MeOH at 110 °C for 10 minutes under microwave conditions (Scheme 1A).[11] With dimer **6** in hand, we hoped that addition of the monomeric ligand **3** to the crude reaction mixture would directly yield the desired complex **7**. However, under a range of conditions, even in the presence of various organic and inorganic bases, this failed to generate any adduct. It was found necessary to first evaporate the MeOH and then redissolve the complex in DCM. Subsequent treatment of this solution with either $NaOAc{\cdot}3H_2O$ or Bu_4NOAc (TBAA) in the presence of monomer **3** cleanly furnished the desired complex **7** in quantitative conversion. Experiments carried out in the absence of base failed to show any reaction. If required, the ligated complex **7** could also be easily purified by column chromatography on silica using a 9 : 1 hexane–EtOAc (R_f 0.32) solvent system, affording 94–96% isolated yield of **7**.

An initial comparative test of the catalytic activity of the parent complex **1** alongside the new vinyl analogue **7** was undertaken in batch. In parallel experiments benzaldehyde and acetophenone (1 mmol) were heated at reflux in iPrOH with 3 mol% of complex (**1** or **7**) and 5 mol% of *t*BuOK. After 3 h the reactions were stopped and analysed, pleasingly only the presence of the corresponding alcohols were detected in each of the four vessels. This result encouraged us to further progress the study.

Many immobilised catalysts are limited in their substrate scope as they suffer from metal leaching induced by competitive ligand exchange. This is especially true for heterocyclic substrates commonly found in many pharmaceutical and agrochemicals, where exchange and sequestration from the solid phase is a notorious problem. Therefore to quickly assess the stability of complex **7** and evaluate the potential for deleterious ligand exchange, we conducted several experiments using various chelating ligands including under simulated reaction conditions. As an illustration, solutions of complex **7** and 2-phenylpyridine (equimolar) were heated at 60–100 °C (5 °C increments) for 1, 4, 12 and 24, 120 h in iPrOH and acetone with additionally added *t*BuOK (20 mol%) or tetraethylammonium formate (2 equiv.). In all cases no evidence was found by NMR or MS for ligand exchange. In the cases of reactions involving iPrOH, small amounts of acetone were detected in the crude reactions, although this was not quantified. Having established the general stability of the complex we next turned our attention to the formation of the monolith.

To make the most effective use of the valuable precursor complex **6** we elected to pursue a strategy involving initial polymerisation of ligand **3** within a monolith followed by a flow based loading of the iridium complex. Using a Vapourtec R4 unit we were able to rapidly screen conditions for the monolith formation and successive iridium loading. The formation of the monolith takes place inside a sealed column (Omnifit column with fixed end pieces) using an initially homogeneous mixture of the functionalised monovinyl monomer **3**, styrene, divinylbenzene, a porogenic solvent (dodecanol) and a radical initiator, namely 4,4′-azobis(4-cyanovaleric acid). Radical polymerisation was induced at elevated temperatures (>90 °C using the Vapourtec air heating system) generating a rigid monolithic matrix possessing high levels of crosslinking (Fig. 2). The porogen and any residual non-polymeric material can be easily flushed out leaving a porous functionalised monolith by attaching the column in-line to the Vapourtec solvent delivery system.

Two monolith column sizes were prepared; 6.6 × 50 mm column equating to a dry polymer weight of 0.73 g (theoretical loading of 0.44 mmol ligand) and a larger 10 × 100 mm column with a dry polymer mass of 4.82 g (theoretical loading of 3.2 mmol ligand); four monoliths were made simultaneously using a single Vapourtec R4 system. Following washing, the monoliths were loaded with iridium by eluting a solution of complex **6** and equimolar TBAA in DCM (0.05 M;



Monomer 3	Styene	DVB	Dodecanol	Initiator
12%	12%	18%	57%	1%

Fig. 2 Top image: White column containing polymerised monolith. Yellow column containing Iridium loaded monolith. Bottom image: Monolith composition (wt%).

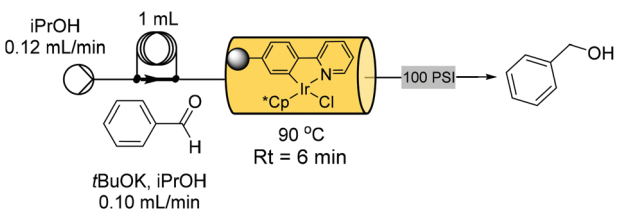
flow rate 0.15 mL min^{-1}) through the cartridge using a recycling strategy (total time 20 h). The solution was then changed to neat DCM and the column washed for a further 4 h.

Based upon inductively coupled plasma-mass spectroscopy (ICP-MS) iridium analysis, an accumulated iridium content of 0.33 (±0.04–4 columns) and 2.54 (± 0.19–3 columns) mmol for the two column sizes was achieved. Using alternative solvents or heating the column during loading failed to improve upon these loadings which are 75% (small; 6.6 × 50 mm) and 79% (large; 10 × 100 mm) of the theoretical maximum.

To test the monoliths, we placed one of the small units (0.73 g, 0.44 mmol theoretical) into the flow path of a Uniqsis FlowSyn (Scheme 2). A 1 mL aliquot of benzaldehyde (1.5 M) containing 3 mol% *t*BuOK in iPrOH was injected into the flow path and directed through the monolith, which was heated to 90 °C, at a flow rate of 0.12 mL min^{-1}, giving a residence time of approximately 6 minutes. This led to complete conversion to the corresponding alcohol with an effective catalyst loading of ~35 mol% (theoretical or 26% corrected based upon ICP-MS). Injecting a further 5 repeat plugs of the benzaldehyde solution each gave complete conversion to benzyl alcohol demonstrating the immobilised iridium species functioned catalytically. Also, no iridium species were found on analysis of the final solutions by MS. Next, we examined the reduction of acetophenone, a substrate which is known to require longer reaction times, using the same column reactor. At a flow rate of 0.12 mL min^{-1}, 42% conversion to 1-phenylethanol was achieved. Reducing the flow rate to 0.08 mL min^{-1} gave a corresponding increase to 62% conversion. A total of 93% conversion was obtained at a flow rate of 0.05 mL min^{-1}, the practical limit of the Uniqsis system for pumping. By demonstration, diluting the input of the acetophenone (to 1 M) allowed complete conversion to the alcohol at a flow rate of 0.05 mL min^{-1}. Importantly, the addition of base to the solution of the starting material was found to be vital for these transformations; experiments performed without *t*BuOK or mixing a solution of base injected from an additional sample loop led to unreacted starting materials being isolated.

Having obtained these preliminary results relating to redox reduction, we next investigated the inverse oxidation process. A 1 M solution of 1-phenylethanol in acetone containing 3 mol% Cs_2CO_3 was passed through the monolith (0.1 mL min^{-1}), which was heated at 60 °C. However, this failed to yield any of the desired ketone. Similarly no conversion was obtained when *t*BuOK, DBU or pyridine were used as bases or when the temperature of the reactor was raised to 90 °C. In each case, only crude aldol adducts resulting from acetone enolate attack could be identified by ^{1}H-NMR and GC-MS. During the course of this investigation, we subsequently uncovered a publication by Fujita *et al.* where the parent dimer complex **1** had previously been tested in the oxidation of benzyl alcohol but showed little activity (8% after 20 h).[12] In additional testing we also confirmed that both complex **1** and its derivative **7** showed negligible activity for the oxidation of either benzyl alcohol or 1-phenylethanol using acetone as the reciprocal partner (<4%). Of some note was that on injecting further runs of benzaldehyde and acetophenone through the same small monolith reactor in iPrOH we were again able to obtain complete reduction, confirming that it was still active.

To evaluate the full utility of the flow reactor we set up a flow system with an autosampler input and a fraction collector output (Uniqsis ALF system). This was used in two modes (Fig. 3). First, we placed a new 10 × 100 mm iridium cartridge into the system and started a continuous flow of 4-chloroacetophenone (1 M in iPrOH containing 3 mol% tBuOK) at a rate of 0.10 ml min^{-1} (residence time of 52 min) through the reactor. The fraction collector was used to aliquot 5 mL samples, which were individually analysed. The first sample through the system showed only 18% conversion, the second 83% but by



Scheme 2 Monolith reactor testing configuration.

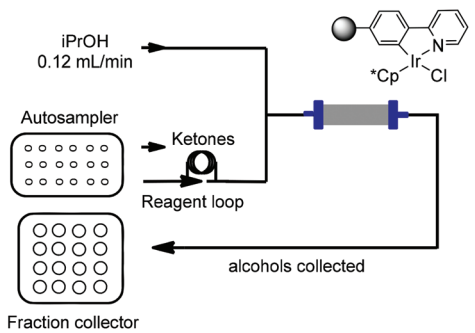


Fig. 3 Flow reactor with autosampler and fraction collection.

the third sample quantitative conversion was reached. We collected a further total of 112 samples, each of which showed complete conversion, before stopping the reactor after 100 h whilst still at full conversion. This equates to 0.56 M of substrate processed using 2.54 mmol of immobilised catalyst, giving a catalyst turnover of 220 and a catalyst usage of 0.45 mol%. To validate this result, a new cartridge was placed in-line and the reaction repeated using acetophenone. Apart from a slightly longer induction phase until it reached full conversion the system behaved identically, processing over 600 mmol of substrate before being stopped still functioning at full catalytic activity.

We also wished to test the extent of the substrate scope by setting the reactor to automatically progress through a small library of starting materials. To this end, a collection of 40 aldehydes and ketones were prepared as 1.5 M stock solutions. These were loaded into the autosampler. Each sample was then processed consecutively using a 5 mL sample injection (7.5 mmol) followed by a 15 mL iPrOH wash, which was collected as a single combined fraction for analysis by ^{1}H-NMR. For consistency purposes each sample was run in duplicate in a randomised sequence[13] (Table 1).

As can be seen from the tabulated data, the reactor showed excellent activity with most substrates, giving full conversion.[13] Both benzylic and aliphatic aldehydes and ketones were successfully reduced. However, a number of substrates (entries 11, 15, 22, 23, 26, 29, 32 and 37) required extended residence times in order to obtain complete conversion. This was achieved by simply reducing the flow rate to 0.12 mL min^{-1}, giving a doubled residence time which allowed these less reactive compounds to be fully transformed. An exception was entry 28, which failed to show any improvement at reduced flow rates. Indeed, the same conversion of ~95% was obtained even at a flow rate of 0.5 mL min^{-1} and residence time of only 15 min.[14] In addition, a notable few materials (entries 10 and 21) failed to show any reaction allowing partial recovery of the starting materials. In each instance the compounds possess an acidic hydrogen. This is also consistent with the results obtained from the phenolic compound entry 8, which showed low conversions even using extended reaction times. It was also identified that these compounds (entries 8, 10 and 21) were retained within the reactor, causing cross contamination of latter samples by slow leaching of the compound into the flow stream. The compounds also retarded the activity of the reactor until they had been fully purged from the system. In a separate reaction, we showed that 4-bromobenzaldehyde in the presence of 25 mol% of 4-chlorophenol using 3 mol% *t*BuOK gave only 3 and 6% conversion respectively under the previously successful conditions. It is difficult to access if this result is simply a problem of depletion of the base (pK_a of the phenol) inhibiting the reaction. However, extensive retention of the phenol components by the reactor cartridge indicates indirectly a stronger interaction with the immobilised catalyst. In support of this hypothesis, a non-iridium loaded monolithic cartridge showed no chromatographic retention of 4-chlorophenol.

Finally, α,β-unsaturated ketones failed to give any carbonyl reduction; instead small quantities of the product derived from hydride conjugate addition were detected in the reaction mixtures although this was not significant (entries 9 and 34). The vinylogous amide (entry 35) being a more electron rich system gave no detectable reaction. This is consistent with a system requirement for a more electron deficient carbonyl for effective reduction.

During our testing we also made two additional discoveries regarding the storage and stability of the immobilised catalyst. It was found that if the catalyst was stored in iPrOH or with residual alcohol still present from its use in the reduction reactions, this led to its deactivation after only a few hours. This was immediately identifiable as the cartridge change from the standard characteristic canary yellow to a more golden orange in colour.

This visual indicator was consistent with significantly reduced activity. A previously used cartridge stored in iPrOH overnight gave only 6% conversion of benzaldehyde to benzyl alcohol (10 × 100 mm, 3 mol% *t*BuOK, 90 °C; 0.25 mL min^{-1}). After equivalent storage for 3 days in iPrOH the cartridge gave no activity. Interestingly, a fresh column could be washed and stored in iPrOH without any dertious results (10 × 100 mm, 3 mol% *t*BuOK, 90 °C; 0.25 mL min^{-1} – quantitative conversion). However, adding any form of base to the iPrOH storage solution (*t*BuOK, NaOMe) resulted in slow deactivation. This was also found to be the case if EtOH or MeOH was used although the deactivation took much longer, 5 and 8 days respectively which is in accordance with their relative oxidation potentials. We account for this behaviour by assuming that a iridium hydride like species formed from abstraction of a hydrogen from an alcohol under basic conditions eventually undergoes a competitive reductive elimination in the absence of a carbonyl acceptor, leading to a reduced and inactive iridium species. As a result of these observations we determined that post-washing and storage of the reaction cartridge in acetone stabilised the catalyst. After 3 days, a cartridge stored in acetone could be used again with no discernible difference in reactivity. However, indefinite storage of used monoliths was found not to be possible, with cartridges stored for >12 days showing gradual and accelerated deactivation being completely inactive after 3 weeks.

Our final assessment was to determine the extent of metal leaching during a extended run. For this experiment, a freshly prepared and washed cartridge (10 × 100 mm) was inserted in-line and a 1.35 M solution of 3-chloroacetophenone (3 mol% *t*BuOK) was eluted through the monolith (heated at 90 °C) as a continuous flow (0.25 mL min^{-1}). The output was collected as 200 mL fractions, which were concentrated under reduced pressure and analysed for conversion. The catalyst performed well, allowing a total processed volume of 1.4 L in >98% conversion as determined by ^{1}H-NMR (93.3 h, 1.89 M processed, TON 744, 2.45 mmol of catalyst −0.13 mol% of catalyst usage). A gradual deactivation of the system was observed linearly over the next 6 samples (1.62 M), decreasing the conversion to 92%. A further more rapid reduction in the conversion was observed over the next 7 samples (1.89 M), reducing the conversion to 77% when the reactor was manually stopped. This again

Table 1 Library production using an iridium catalyst monolith reactor

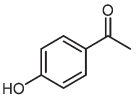
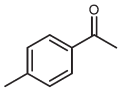
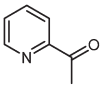
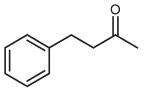
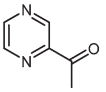
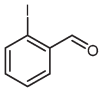
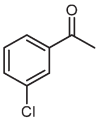
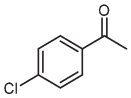
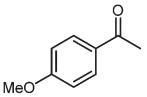
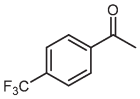
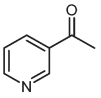
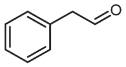
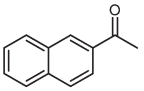
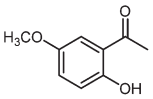
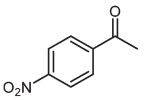
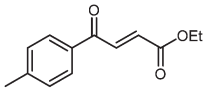
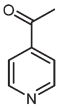
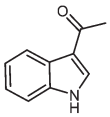
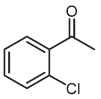
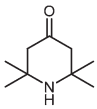
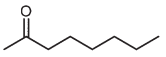
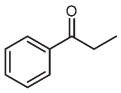
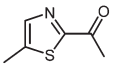
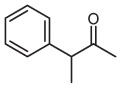
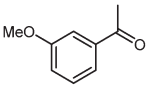
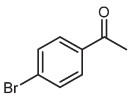
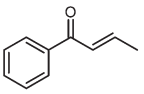
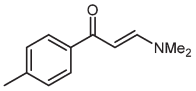
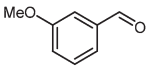
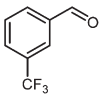
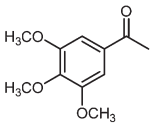
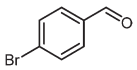
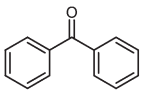
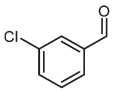
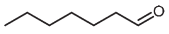
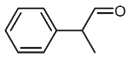
Entry	Substrate	Conversion[a] (run no.)	Entry	Substrate	Conversion[a] (run no.)
1		100% (1, 58)	21		0%, (12)[d] *only 42% SM recovery*
2		100% (2, 79)	22		55% (13)[e], 94% (61), 100%[c]
3		100% (3, 42)	23		72% (14), 74% (48)
4		100% (4, 60)	24		100% (15, 66)
5		100% (5, 63)	25		100% (16, 75)
6		100% (6, 68)	26		90% (17), 85% (57), 100%[c]
7		100% (7, 73)	27		100% (18, 50)
8		18% (8)[d] *only 57% SM recovery* 24%[c]	28		95% (19), 96% (44), 94%[c]
9		33% (9)[b,e], 28 (54)[b]	29		47% (20), 49% (77), 100%[c]
10		0% (10)[d] *only 71% SM recovery*	30		100% (21, 80)
11		42% (11)[e], 82% (41), 100%[c]	31		100% (22, 76)
12		98% (23), 100% (67)	32		76% (32), 79% (51), 100%[c]
13		100% (24, 45)	33		100% (33, 53)
14		97% (25), 100% (52)	34		5% (34)[b], 7 (46)[b]

Table 1 *(Contd.)*

Entry	Substrate	Conversion[a] (run no.)	Entry	Substrate	Conversion[a] (run no.)
15		43% (26), 38% (43), 100%[c]	35		0% (35, 78), 0%[c]
16		100% (27, 47)	36		100% (36, 69)
17		100% (28, 70)	37		44% (37), 48% (71), 100%[c]
18		100% (29, 59)	38		100% (38, 64)
19		100% (30, 76)	39		100% (39, 72)
20		100% (31), 97% (62)	40		100% (40, 55)

[a] 1.5 M in iPrOH with 3 mol% *t*BuOK; flow rate 0.25 mL min^{-1}, residence time ~32 min; reactor heated at 90 °C. [b] GC-MS analysis of the reaction mixture indicated conjugate addition, the reaction was not analysed by NMR. [c] Flow rate 0.12 mL, residence time ~65 min. [d] Duplicate reactions were not run due to cross contamination issues. [e] Sample contaminated with starting material from previous run. The reactor was stopped and purged by flowing iPrOH at a flow rate of 0.5 mL min^{-1} for 1 h.

coincided with an observable colour change of the monolith reactor (canary yellow → pale orange). As a simple proof of concept, one incomplete 200 mL reaction sample of 78% conversion was passed through a new monolith reactor under identical processing conditions, giving full conversion upon ^{1}H-NMR analysis. In addition six samples (1, 8, 10, 14, 17 and 20) were selected for ICP-MS analysis. It was found that none of the concentrated samples contained any iridium (at the limits of detection used <0.1 ppm), which confirms the strong retention of the iridium within the polymer ligating matrix.

Conclusions

In conclusion, we have successfully prepared a monolithic iridium hydride transfer catalyst which has shown high activity and excellent retention of the metal under flow processing conditions. We have been able to demonstrate its use in a series of transfer reductions of aldehydes and ketones comprising both aliphatic and benzylic chemical structures. A limitation regarding the processing of substrates containing phenolic and N–H indole functional groups was identified. We have furthermore conducted several scale-up experiments exploring the processing potential of these small scale monoliths.

Experimental

General information

Unless otherwise specified, reagents were obtained from commercial sources and used without further purification. Solvents were obtained from Fisher Scientific and distilled before use. ^{1}H-NMR spectra were recorded on a Bruker Avance DPX-400, with the residual solvent peak as the internal reference ($CDCl_3$ = 7.26 ppm). ^{13}C-NMR spectra were recorded on the same spectrometer with the central resonance of the solvent peak as the internal reference ($CDCl_3$ = 77.16 ppm). IR spectra were recorded neat on a PerkinElmer Spectrum One FTIR spectrometer with Universal ATR sampling accessories. Letters in parentheses refer to the relative absorbance of the peak: w = weak (<40% of the most intense peak), m = medium (40%–70% of the most intense peak), s = strong (>70% of the most intense peak). High resolution mass spectra (HRMS) were recorded on a Waters Micromass LCT Premier Q-TOF spectrometer by electrospray ionisation (ESI) or an ABI/MDS Sciex Q-STAR Pulsar. The mass reported is containing the most abundant isotopes. Limit: ±5 ppm. LC-MS analysis was performed on an Agilent HP 1100 series chromatograph (Mercury Luna 3μ C18 (2) column) attached to a Waters ZQ2000 mass spectrometer with ESCi ionisation source in ESI mode. Microwave assisted reactions were performed in a Biotage Initiator microwave device (see http://www.biotage.com/). Elemental analysis

and ICP-MS was performed at Butterworth Laboratories Ltd. Samples were run in triplicate and are taken as averages of the 3 runs. Digestion was conducted by microwave (BLM486G).

VapourTec® R2+ R4 unit: (see http://www.vapourtec.co.uk)

The R2+ unit consists of two HPLC pumps that can be easily monitored and adjusted. The pumps can operate between reaction pressures of 1–50 bar and flow rates of 0.05–10.0 mL min^{-1} per channel with easy switching between reagent and solvent inputs. Reagent addition can be achieved *via* a continuous mode by passage of a stock solution through the pump heads or employing single alloquot injection *via* the two in-line sample loops. The R4 is a heater unit, which can accommodate up to four independently heated reactors. Precise temperature control and measurement is possible over the temperature range of ambient to 150 °C (Fig. 4). Very high heating and cooling rates (up to 80 °C min^{-1}) allow for quick temperature changes. Glass Omnifit® columns and supplied housing were used to prepare the monoliths as previously described.[8]

Uniqsis unit: (see http://www.uniqsis.com)

The FlowSyn PEEK unit consists of two independently controlled HPLC pumps with PEEK channeled flow paths which can operate at reaction pressures of up to 70 bar and flow rates of 0.05–10.0 mL min^{-1} per pump head. Each channel can be easily switched between a reagent or solvent supply. Reagent addition can be conducted in a continuous manner by elution of a stock solution through the pump heads or as a plug flow by employing two in-line injection sample loops. The FlowSyn includes two heatable reactor modules: a convective heating coil and a column holder, which can be heated up to 260 °C. Glass Omnifit® columns and backpressure regulators were used to perform the experiments.

The FlowSyn Automated Loop Filling (FlowSyn Auto-LF) (Fig. 5) is a module which includes an auto-sampler and a fraction collector, allowing the preparation of libraries. It loads and collects reactions simultaneously, integrating wash steps to prevent cross-contamination using a Gilson 10 ml Syringe pump. The solutions of the starting materials are prepared in vials including septum-protected caps and loaded into an intermediate holding coil, which incorporates air bubbles to prevent sample dispersion and dilution, and directly transferred to the sample loops. The final products are collected using a rack of vials. The module also includes a laptop with software for both programming and real-time monitoring of the experiments (pressure and temperature plots), generating a sounding alarm when the pressure of the system drops due to air bubbles and giving 1 min to purge the pumps before the system stops.

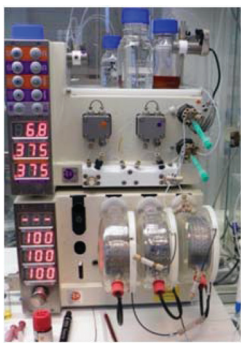


Fig. 4 VapourTec® R2+ R4 unit.

Fig. 5 Uniqsis FlowSyn unit with ALF automation.

General procedures

Preparation of 2-(4-vinylphenyl)pyridine monomer (3). Procedure A: A mixture of 4-vinylbenzyl boronic acid (1.03 g, 7 mmol), Cs_2CO_3 (2.60 g, 8 mmol) and 2-bromopyridine (0.79 g, 5 mmol) were dissolved in solvent mixture of toluene–EtOH (10 : 1 mixture, 40 mL) and tetrakis-triphenylphosphine palladium(0) was added (0.29 g, 0.25 mmol). The mixture (which changed from bright yellow to orange) was degassed and stirred under nitrogen while heated at 100 °C for 6 hours. The reaction was then quenched by addition of water and extracted with EtOAc (filtration over celite or a plug of silica was used to remove insoluble palladium residues). The organics were dried over anhydrous $MgSO_4$ and the solvent concentrated under vacuum. The crude product was purified by column chromatography, eluting with hexane–EtOAc (95 : 5) to give the desired monomer as a colourless oil (750 mg, 83% yield).

Procedure B *via* microwave-assisted reaction: Into a 20 mL microwave vial was added 4-vinylbenzyl boronic acid (740 mg, 5 mmol), Cs_2CO_3 (1.79 g, 5.5 mmol) and 2-bromopyridine (569 mg, 3.6 mmol) and dissolved in toluene–EtOH (10 : 1 mixture, 20 mL). Tetrakis-triphenylphosphine palladium(0) was added (0.29 g, 0.25 mmol) and the mixture (which changed from bright yellow to orange) was heated at 120 °C for 30 min using a Biotage Initiator microwave device. The reaction was quenched by addition of water and the crude treated as described in the procedure above to yield the desired monomer as colourless oil (560 mg, 86% yield).

2-(4-Vinylphenyl)pyridine. ^{1}H NMR (400 MHz, $CDCl_3$, δ/ppm, J/Hz): 8.70 (1H, d, J = 4.6, HetAr), 8.01 (2H, d, J = 8.1, Ar), 7.68–7.62 (2H, m, HetAr), 7.52 (2H, d, J = 8.4, Ar), 7.17–7.13 (1H, m, HetAr), 6.77 (1H, dd, J = 17.5, 10.9, –C*H*═CH_2), 5.83 (1H, dd, J = 7.5, 0.7, –CH═CH_2), 5.30 (1H, dd, J = 11.0, 0.9, –CH═CH_2). ^{13}C NMR (100 MHz, $CDCl_3$, δ/ppm, J/Hz) 156.82 (C), 149.67 (CH), 138.69 (C), 138.17 (C), 136.73 (CH), 136.43 (CH), 127.05 (2 × CH), 126.67 (2 × CH), 122.12 (CH), 114.53 (CH_2). IR (ν_{max}/cm^{-1}): 3049.2 (w), 3011.5 (w), 1628.6 (w), 1588.2 (m), 1572.9 (m), 1466.7 (m), 1435.2 (m), 1297.6 (w), 1265.0 (m), 1153 (w), 1013.2 (w), 989.2 (m), 907.5 (s), 851.4 8s), 786.0 (s),

731.9 (s), 703.7 (m). HRMS (*m*/*z*) calculated for $C_{12}H_{13}N_2$ (M + H), 182.0973; found 182.0970. Anal. Calculated for $C_{13}H_{11}N$: C, 86.15; H, 6.12; N, 7.73. Found: C, 86.16; H, 6.23; N, 7.69. No P found.

Procedure for the preparation of pyridinyl Ir complex (7)

*Synthesis of Chloro(pentamethylcyclopentadienyl)iridium(III) dimer (**6**) [Ir(Cp*Cl$_2$)$_2$].* A mixture of $IrCl_3{\cdot}3H_2O$ (500 mg, 1.35 mmol) and pentamethylcyclopentadiene (0.375 mL, 2.4 mmol) was dissolved in methanol (6 ml, generating a dark green-black solution) and heated at 110 °C with very high absorption for 10 min using a Biotage Initiator microwave device. The bright orange precipitate formed was filtered and washed with fresh methanol (2 × 5 mL) to furnish pure Ir(Cp*Cl$_2$)$_2$. Spectroscopic data was consistent with literature values.

Formation of ligated complex (7). A mixture of $[Cp^*IrCl_2]_2$ (100 mg, 0.125 mmol), 2-(4-vinylphenyl)pyridine (45 mg, 0.25 mmol) and $NaOAc{\cdot}3H_2O$ (85 mg, 0.625 mmol) [alternatively $(Bu)_4NOAc$ (188 mg, 0.625 mmol) can be used] was dissolved in dichloromethane (5 mL) and stirred at room temperature under argon for 24 h. The crude mixture was filtered through celite to remove the base and the resultant red solution was concentrated under vacuum. The product was then washed with hexane to give the desired complex as a bright orange solid in quantitative yield.

Chloro(pentamethylcyclopentadienyl)[(2-pyridinyl)4-vinylphenyl]iridium(III) (7). ^{1}H NMR (400 MHz, $CDCl_3$, δ/ppm, *J*/Hz): 8.66 (1H, d, *J* = 5.5, Ar), 7.84 (1H, s, Ar), 7.76 (1H, d, *J* = 8.0, Ar), 7.63–7.59 (2H, m, Ar), 7.11 (1H, d, *J* = 8.1, Ar), 7.12–7.03 (1H, m, Ar), 6.78 (1H, dd, *J* = 17.6, 11.0, –C*H*=CH$_2$), 5.81 (1H, d, *J* = 17.5, –CH=C*H*$_2$), 5.26 (1H, d, *J* = 17.7, –CH=C*H*$_2$), 1.72 (15H, s, Cp*); ^{13}C NMR (100 MHz, $CDCl_3$, δ/ppm): 166.9 (C), 163.3 (C), 151.4 (CH), 144.1 (C), 139.4 (CH), 137.3 (CH), 137.0 (C), 133.9 (CH), 123.9 (CH), 122.2 (CH), 120.3 (CH), 119.0 (CH), 113.7 (CH_2), 88.5 (*Cp**Me$_5$), 8.97 (Cp**Me*$_5$). HRMS (*m*/*z*) calculated for $C_{23}H_{26}NClIr$ (M + H), 544.1378; found 544.1370.

Monolith preparation

General procedure for the polymerisation. The monoliths were prepared according with the following general procedure. The reaction scale specified below (4.8 g of mixture) provides sufficient monolith material to fill a 10 mm i.d. × 100 mm Omnifit® glass column. Technical grade solution (80%) of divinylbenzene (DVB) containing a mixture of isomers was used and percentages are given on a w/w basis (reagent/total mixture).

To a mixture of the functionalised monovinyl monomer **3** (576 mg, 3.2 mmol, 12%), styrene (0.636 mL, 0.578 g, 5.54 mmol, 12%), DVB (0.945 mL, 0.864 g, 6.64 mmol, 18%), dodecanol (3.34 mL, 57%) was added 1,1′-azobis(cyclohexanecarbonitrile) (0.24 g, 1.0% relative to monomer + styrene + DVB). The mixture was vigorously stirred trying to dissolve the initiator and a 10 mm i.d × 100 mm Omnifit glass column was filled from this colourless, clear solution. Both ends of the columns were sealed using PTFE plugs and the VapourTec R4 convective heating unit was used to heat the column at 90 °C during 20 h. The resulted white polymeric monolith was washed with dry THF at 0.1–1 mL min^{-1} (40 min ramp) for 2 h at 60 °C using the R2+ and R4 combination unit. The back-pressure for the washing step was 1–2 bars and no monomer was observed when the output solution was analysed by LC-MS or ^{1}H-NMR. Elemental analysis: Found C, 90.80; H, 6.91; N, 2.17 (3.12 mmol calculated loading based upon N content).

General procedure for the loading of the monolith. A stock solution (0.05 M) of iridium dimer **6** (570 mg, 3.2 mmol) and equimolar tetrabutyl ammonium acetate in dry dichloromethane were maintained under an N_2 atmosphere and pumped continuously through the monolith column prepared in the previous step over 20 h at a flow rate of 0.15 mL min^{-1} using the Uniqsis FlowSyn device. The monolith turned from white to yellow (see Fig. 2 main body text) and the Ir loading was calculated by inductively coupled plasma-mass spectroscopy (ICP-MS) iridium analysis: calculated (small column 6.6 × 50 mm) iridium content 0.33 mmol (±0.04–4 columns), (large column 10 × 100 mm) iridium content 2.54 mmol (±0.19–3 columns).

Transfer hydrogenation in flow

A set of carbonyl derivatives were reduced in flow according to the following procedures.

General procedure for individual experiments. A solution of the carbonyl containing 3 mol% *t*BuOK in iPrOH was injected into the sample loop of the Uniqsis FlowSyn device. The valve was set to load and the material pumped through the monolith, which was heated at 90 °C, using iPrOH as the system solvent. The output of the reactor was directed through a column packed with a solid-supported sulfonic acid (Amberlyst A15 6.2 g) to sequester the base and a back-pressure regulator (100 psi) was added in-line. The output of the reactor was collected as a single fraction and the solvent evaporated to yield the corresponding alcohol which was immediately analysed.

Benzyl alcohol

Prepared from a solution of benzaldehyde in iPrOH (1.5 M, 2 mL), which was injected and passed through the monolith (0.7 g, 0.44 mmol theoretical loading) at a flow rate of 0.12 ml min^{-1} (residence time of approximately 6 minutes). The output from the reactor was collected for 80 min, giving enough time to wash the column once the reaction was finished. The alcohol was obtained in quantitative yield and NMR data was consistent with literature values.

1-Phenylethanol

Prepared from a solution of acetophenone in iPrOH (1.5 M, 2 mL), which was injected and passed through the monolith (0.7 g, 0.44 mmol theoretical loading) at a flow rate of 0.05 ml min^{-1} (residence time of approximately 14 minutes). The output from the reactor was collected for 80 min, giving enough time to wash the column once the reaction was

finished. The alcohol was obtained in quantitative yield and NMR data was consistent with literature values.

General procedure for experiments using a single input and a fraction collector. The fraction collector and the laptop were connected to the FlowSyn reactor and the ALF software used to program the experiment to run with a continuous input of starting material and the product to be collected in 5 mL fractions. A stock solution of the 4-chloroacetophenone (1 M in iPrOH) containing 3 mol% *t*BuOK was pumped continuously (flow rate 0.10 ml min^{-1}, residence time 52 min) through a new monolith (10 × 10 mm i.d., 4.82 g, theoretical loading of 2.54 mmol), which had previously been washed with fresh iPrOH. The column was heated to 90 °C and the output collected into a rack of vials which were individually analysed by NMR. **4-Chloro-1-phenyl ethanol:** Obtained as a pale brown oil. ^{1}H NMR (400 MHz, $CDCl_3$, δ/ppm, J/Hz): 7.34–7.30 (4H, m, Ar), 4.90–4.85 (1H, m, –C*H*), 2.14 (1H, OH), 1.48 (3H, d, J = 6.6, –CH_3); ^{13}C NMR (100 MHz, $CDCl_3$, δ/ppm): 144.3 (C), 133.1 (C–Cl), 128.6 (2 × CH), 126.8 (2 × CH), 69.7 (CH–OH), 25.3 (CH_3).

General procedure for the preparation of a library of compounds using automated injection and a fraction collector. The FlowSyn Automated Loop Filling (FlowSyn Auto-LF) module was connected to the flow reactor and programmed using the laptop, so the conditions and reagent rack layout for each experiment were established. A new monolith (10 × 10 mm i.d., 4.82 g, theoretical loading of 3.2 mmol) was attached to the system and washed with fresh iPrOH. Stock solutions of the starting materials (1.5 M in iPrOH, 12 mL) containing 3 mol% *t*BuOK were placed in the sample rack, and loaded *via* the 5 mL holding coil, with air bubbles incorporated in between samples to avoid dispersion. Reagent solutions were transferred directly to the sample loops of the Uniqsis reactor and pumped through the monolith, which was heated at 90 °C, at a flow rate of 0.25 mL min^{-1} using iPrOH as the system solvent. The experiment was set up so that the output was collected as 20 mL fractions (5 mL experiment + 15 mL wash), which were individually analysed by NMR. The software provided real-time monitoring, with pressure and temperature plots ensuring that the system was stable all over the run. Each experiment was run in duplicate in a random sequence. Compounds were assessed for conversion by comparison to authentic samples of the starting material and product. Yield was determined by gravimetric assessment of the evaporated samples and comparison against authentic sample.

Acknowledgements

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Notes and references

1 For reviews on transition metal hydrogen transfer catalyzed reactions see: (*a*) J. S. M. Samec, J.-E. Bäckvall, P. G. Andersson and P. Brandt, *Chem. Soc. Rev.*, 2006, **35**, 237–248; (*b*) T. Ikariya and A. J. Blacker, *Acc. Chem. Res.*, 2007, **40**, 1300–1308; (*c*) M. H. S. A. Hamid, P. A. Slatford and J. M. J. Williams, *Adv. Synth. Catal.*, 2007, **349**, 1555–1575; (*d*) T. Suzuki, *Chem. Rev.*, 2011, **111**, 1825–1845; (*e*) C. Mazet, *Chimia*, 2011, **65**, 802–805.

2 (*a*) G. Z. Wang, U. Andreasson and J. E. Backvall, *J. Chem. Soc., Chem. Commun.*, 1994, 1037–1038; (*b*) U. Karlsson, G. Z. Wang and J. E. Backvall, *J. Org. Chem.*, 1994, **59**, 1196–1198; (*c*) A. M. Hayes, D. J. Morris, G. J. Clarkson and M. Wills, *J. Am. Chem. Soc.*, 2005, **127**, 7318–7319; (*d*) X. Wu and J. Xiao, *Chem. Commun.*, 2007, 2449–2466; K. Fujita, N. Tanino and R. Yamaguchi, *Org. Lett.*, 2007, **9**, 109–111; (*e*) K. Fujita, Y. Enoki and R. Yamaguchi, *Tetrahedron*, 2008, **64**, 1943–1954; (*f*) O. Saidi, A. J. Blacker, M. M. Farah, S. P. Marsden and J. M. J. Williams, *Angew. Chem., Int. Ed.*, 2009, **48**, 7375–7378; (*g*) M. Ito, Y. Endo, N. Tejima and T. Ikariya, *Organometallics*, 2010, **29**, 2397–2399; (*h*) O. Saidi, A. J. Blacker, M. M. Farah, S. P. Marsden and J. M. J. Williams, *Chem. Commun.*, 2010, **46**, 1541–1543.

3 (*a*) M. A. Berliner, S. P. A. Dubant, T. Makowski, K. Ng, B. Sitter, C. Wager and Y. Zhang, *Org. Process Res. Dev.*, 2011, **15**, 1052–1062.

4 (*a*) D. J. Bayston, C. B. Travers and M. E. C. Polywka, *Tetrahedron: Asymmetry*, 1998, **9**, 2015–2018; (*b*) Y. C. Chen, T. F. Wu, J. G. Deng, H. Liu, X. Cui, J. Zhu, Y. Z. Jiang, M. C. Choi and A. S. Chan, *J. Org. Chem.*, 2002, **67**, 5301–5306; (*c*) X. Li, X. Wu, W. Chen, F. E. Hancock, F. King and J. Xiao, *Org. Lett.*, 2004, **6**, 3321–3324; (*d*) P. N. Liu, J. G. Deng, Y. Q. Tu and S. H. Wang, *Chem. Commun.*, 2004, 2070–2071; (*e*) P. N. Liu, P. M. Gu, J. G. Deng, Y. Q. Tu and Y. P. Ma, *Eur. J. Org. Chem.*, 2005, 3221–3227; (*f*) Y. Arakawa, N. Haraguchi and S. Itsuno, *Tetrahedron Lett.*, 2006, **47**, 3239–3243; (*g*) L. Jiang, T. F. Wu, Y. C. Chen, J. Zhu and J. G. Deng, *Org. Biomol. Chem.*, 2006, **4**, 3319–3324; (*h*) G. H. Liu, J. Y. Wang, T. Z. Huang, X. H. Liang, Y. L. Zhang and H. X. Li, *J. Mater. Chem.*, 2010, **20**, 1970–1975; (*i*) S. J. Lucas, B. D. Crossley, A. J. Pettman, A. D. Vassileiou, T. E. O. Screen, A. J. Blacker and P. C. McGowan, *Chem. Commun.*, 2013, **49**, 5562–5564.

5 (*a*) C. Scheeren, F. Maasarani, A. Hijazi, J. .-P. Djukic, M. Pfeffer, S. D. Zarić, X.-F. Le Goff and L. Ricard, *Organometallics*, 2007, **26**, 3336–3345; (*b*) L. Li, W. W. Brennessel and W. D. Jones, *J. Am. Chem. Soc.*, 2008, **130**, 12414–12419; (*c*) Y. Boutadla, O. Al-Duaji, D. L. Davies, G. A. Griffith and K. Singh, *Organometallics*, 2009, **28**, 433–440.

6 (*a*) J. F. Hull, D. Balcells, J. D. Blakemore, C. D. Incarvito, O. Eisenstein, G. W. Brudvig and R. H. Crabtree, *J. Am. Chem. Soc.*, 2009, **131**, 8730–8731; (*b*) J. D. Blakemore, N. D. Schley, D. Balcells, J. F. Hull, G. W. Olack, C. D. Incarvito, O. Eisenstein, G. W. Brudvig and R. H. Crabtree, *J. Am. Chem. Soc.*, 2010, **132**, 16017–16029.

7 (*a*) F. Svec and J. M. J. Frechet, *Chem. Mater.*, 1995, **7**, 707–715; (*b*) F. Svec and J. M. J. Frechet, *Science*, 1996, **273**,

205–211; (*c*) E. C. Peters, F. Svec and J. M. J. Frechet, *Adv. Mater.*, 1999, **14**, 1169–1181.

8 (*a*) M. Baumann, I. R. Baxendale, S. V. Ley, N. Nikbin and C. D. Smith, *Org. Biomol. Chem.*, 2008, **6**, 1587–1593; (*b*) K. A. Roper, H. Lange, A. Polyzos, M. B. Berry, I. R. Baxendale and S. V. Ley, *Beilstein J. Org. Chem.*, 2011, **7**, 1648–1655; (*c*) C. J. Smith, N. Nikbin, C. D. Smith, S. V. Ley and I. R. Baxendale, *Org. Biomol. Chem.*, 2011, **9**, 1927–1937; (*d*) H. Lange, M. J. Capener, A. X. Jones, C. J. Smith, N. Nikbin, I. R. Baxendale and S. V. Ley, *Synlett*, 2011 (6), 869–873; (*e*) R. J. Ingham, E. Riva, N. Nikbin, I. R. Baxendale and S. V. Ley, *Org. Lett.*, 2012, **14**, 3920–3923.

9 L. Kiwi-Minsker, *Chimia*, 2002, **56**, 143–147.

10 A. Núñez, A. M. Cuadro, J. Alvarez-Builla and J. J. Vaquero, *Org. Lett.*, 2007, **9**, 2977–2980.

11 A. J. Blacker, St. Brown, B. Clique, B. Gourlay, C. E. Headley, S. Ingham, D. Ritson, T. Screen, M. J. Stirling and R. G. Thompson, *Org. Process Res. Dev.*, 2009, **13**, 1370–1378.

12 K.-I. Fujita, T. Yoshida, Y. Imori and R. Yamaguchi, *Org. Lett.*, 2011, **13**, 2278–2281.

13 The random sequence was generated using http://www.random.org/sequences/.

14 We were unable to achieve full conversion with this substrate even under batch conditions. Spectral analysis of the starting material along with m.p. and elemental analysis indicated it was of >99% purity. We can not explain this result at this time.