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Coupling of Heck and hydrogenation reactions in a continuous compact reactor

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ABSTRACT

A continuous multi-step synthesis of 1,2-diphenylethane was performed sequentially in a structured compact reactor. This process involved a Heck C–C coupling reaction followed by the addition of hydrogen to perform reduction of the intermediate obtained in the first step. Both of the reactions were catalysed by microspherical carbon-supported Pd catalysts. Due to the integration of the micro-heat exchanger, the static mixer and the mesoscale packed-bed reaction channel, the compact reactor was proven to be an intensified tool for promoting the reactions. In comparison with the batch reactor, this flow process in the compact reactor was more efficient as: (i) the reaction time was significantly reduced (*ca.* 7 min *versus* several hours), (ii) no additional ligands were used and (iii) the reaction was run at lower operational pressure and temperature. Pd leached in the Heck reaction step was shown to be effectively recovered in the following hydrogenation reaction section and the catalytic activity of the system can be mostly retained by reverse flow operation.

1. Introduction

Microreactor technology (reaction volume ranging in the scale range from nanolitre to millilitre) has gained enormous interest recently in both academic research and practical applications, especially for the fine chemical and pharmaceutical industry [1]. For practical chemical transformations, this engineering technology offers chemistry a potential solution to circumvent limitations of batch processes, such as (i) temperature runaway and poor selectivity in dealing with exothermic reactions, (ii) hot spots due to inefficient mixing, in flow systems, which is often called ‘flow chemistry’.

The advantages of switching conventional batch operations to small flow systems are readily apparent. A prominent benefit of this technology is high surface-to-volume ratio which enables a narrow temperature profile along the reactor and efficient cooling. This feature offers the opportunity to successfully execute highly exothermic/endothermic chemical transformations which are usually inhibited in larger batch reactors. Gross et al. [2] demonstrated the use of a flow reactor in the synthesis of NBI-75043 (an anti-insomnia drug) to promote the key halogen–metal exchange step whose highly exothermic nature limited this total synthesis route in a large-scale batch. Small reaction volume also endows microreaction technology with the inherent safety, which allows us to perform hazardous reactions and reactions using toxic reagents, for instance, selective oxidation of aromatic alcohols by molecular oxygen at up to 24 atm undiluted oxygen pressure [3] and ring-expansion reaction involved diazo compound as a reactant [4]. Another additional interest in flow reactor technology is that, in comparison with batch operation, multi-step synthesis can be more facile to achieve in flow process by dosing reactants in different reaction stages to promote the whole process without either losing valuable unstable intermediates, product isolation at intermediate stages or at least interrupting the whole process. Based on this concept, Baxendale et al. [5] developed a micro-flow process, which involves various packed columns containing immobilized reagents, catalysts, scavengers or catch and release agents, for the multi-step synthesis of the alkaloid natural product oxomaritidine. Moreover, an important advantage of flow chemistry over batch processing is the significant reduction of footprint of transferring technology to production scale due to the principle of numbering up, *i.e.* productivity is increased by simply adding more identical reactors instead of expanding the volume of the reactor [1,6].

In our former study, the use of a multichannel meso-flow compact reactor as a versatile tool for designing practical heterogeneous catalysis process with reasonable throughput was demonstrated. This compact reactor integrated the static mixer and the microchannel heat exchanger which enabled an excellent mixing and heat management ability for efficiently and safely running different kinds of reactions. Several practical examples have

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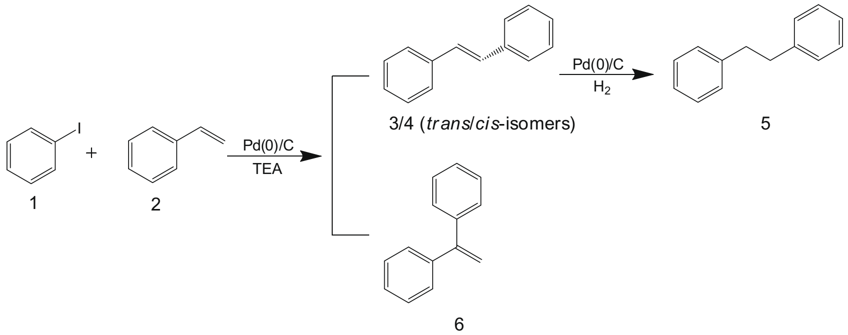

Scheme 1. Consecutive synthesis of 1,2-diphenylethane (**5**).

been successfully demonstrated with this compact reactor, such as (i) selective oxidation [3] and hydrogenation [7] with pure oxygen and hydrogen at elevated pressures, (ii) the staged dosing of gas along the length of the catalytic channel to increase product yield [3,7], (iii) the kinetic study for fast reactions [3,7]. Furthermore, by integrating nanofluids with the micro-heat exchanger, rapid dynamic quenching of chemical reactions was also demonstrated [8].

Following from our previous study, in this work we report the extension in functionality of the compact reactor and have developed of an alternative strategy for continuous multi-step synthesis of 1,2-diphenylethane (an important intermediate for synthesising flame retardants [9]) which is conventionally obtained by a 'one-pot' reaction combining Heck coupling and hydrogenation reactions, Scheme 1.

2. Experimental

2.1. Preparation and characterisation of Pd/C catalyst

The carbon support (~150 μm particle diameter, synthetic carbon manufactured from phenolic resins, MAST Carbons Ltd. Guildford, UK) was dispersed in distilled water (20 mL H_2O for 1.5 g carbon) at a moderate stirring rate under N_2 for 30 min. Aqueous hydrogen tetrachloropalladate(II) (H_2PtCl_6, 50 mL, 14.1 mM, corresponding to 5 wt% of Pd) solution was introduced by portion (10 mL each time) dropwise into the slurry and followed by the addition of aqueous sodium borohydride solution (25 mL, 145 mM, 5 mL each time) under stirring. This sequential introduction of Pd solution and reducing agent was performed incrementally with 10 min break between each addition. The slurry was left for 2 h under a nitrogen atmosphere and gentle stirring. Following impregnation, the suspension was filtered and washed with distilled water several times. The remaining solution was analysed by the atomic absorption spectroscopy (AAS, Perkin Elmer) to determine the quantity of deposited palladium. The catalyst was dried under vacuum at 353 K overnight and stored in a desiccator prior to being used for the reaction studies.

The gas adsorption analysis was performed using a Micromeritrics ASAP 2010 analyser (N_2 as probing gas) for obtaining nitrogen adsorption isotherms to evaluate the specific surface area (S_{BET}), average pore diameter (d) and pore volume (V_p) of the carbon support and catalyst. A relative pressure range of 0.05 to 0.20 was used to calculate the BET surface area. The median pore diameter was calculated from the adsorption branch of the isotherm [10] using the Barrett–Joiner–Halenda (BJH) method (relative pressure range 0.8 to 0.9).

The phase analysis and the determination of the average crystallite size were carried out by X-ray diffraction (XRD) using a Bruker AXS D8 Discoverer X-ray diffractometer, with Cu K_α radiation $\lambda = 0.145$ nm and a graphite monochromator, in the 2θ range of 5° to 75°. The average size of the metal particle was calculated using the Scherrer equation.

2.2. Procedure for batch Heck reactions

Eight millilitres of solvent (anhydrous dimethylformamide, DMF) were first added in a two-necked flask and de-aerated by N_2 flow for 10 min, then 8 mmol of iodobenzene, 12 mmol of styrene, 10 mmol of triethylamine (TEA) and 0.1 mol% of Pd (as heterogeneous catalyst) were introduced into the reactor. The reactor (equipped with a condenser) was placed in a preheated oil bath at 413 K and was vigorously stirred for 4.5 h. Samples were taken at time intervals for off-line GC analysis. All chemicals were purchased from Sigma–Aldrich and used as received.

2.3. Multichannel compact reactor and continuous experiment procedure

The cross-sectional schematic diagram of the compact reactor assembly is shown in Fig. 1. A static mixer was embedded prior to reaction channels to pre-saturate the liquid phase with gaseous reactant before introducing the mixed stream into the reaction channels. The packed-bed channels were imbedded in parallel between the two micro-heat exchangers. The two micro-heat exchangers were located underneath and above all the reaction channels (arranged in cross-flow with respect to the reaction channels).

The reaction channel configuration for consecutive multi-step analysis is shown schematically in Fig. 2. Liquid reagents were premixed and placed in the feed vessels. A HPLC pump (422, Kontron Instruments) was used to flow liquid feed through packed-bed reaction channels, and the product was collected in another vessel via a low dead-volume six-way valve (Valco Instruments) equipped with a 250 μL sample loop. The temperature of the reactor was controlled by using a re-circulating bath (Haake DC30 with Haake B3 tank) to circulate heat transfer fluid (glycerol) through the micro-heat exchangers which were located underneath and above all the reaction channels. Thus, all reaction channels have an even temperature field (the measured temperature differences along the reactor were less than 0.5 K). Each channel was equipped with standard Swagelok® fittings for connecting the liquid and the gas feed lines. The system was pressurised by purging gas (either N_2 or H_2) through the reaction channels and the operating pressure was set by a back pressure regulator (Brooks 5866). Details of the design concepts and the hydrodynamic characteristics of the compact reactor and details of the rig are specified elsewhere [3,11].

2.4. Sample analysis

The analyses of the samples' composition were performed using a Varian chromatograph (CP-3800) equipped with a FID detector

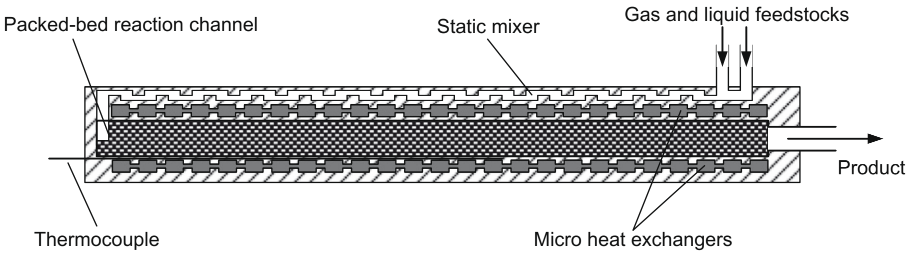

Fig. 1. Schematic cross-sectional diagram of the structured compact reactor.

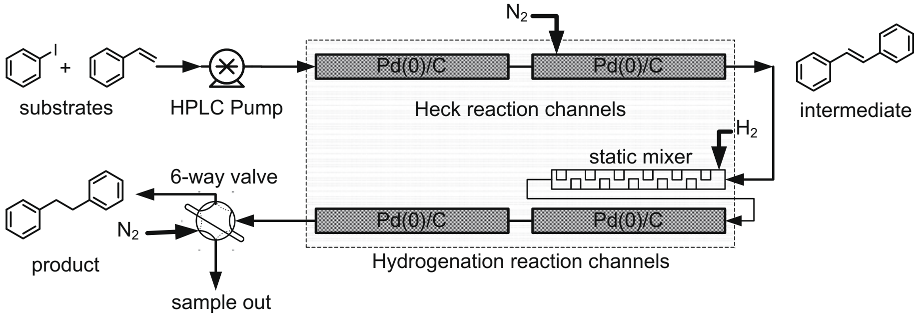

Fig. 2. A schematic diagram of the channel configuration of the compact reactor for consecutive C–C coupling/hydrogenation. The shaded area corresponds to the two micro-heat exchangers located underneath and above all the reaction channels.

and a 15 m capillary column (CP Sil 5 CB, 0.25 mm × 0.25 µm, Varian).

2.5. Determination of Pd leaching

Aliquots of the reaction filtrate (in batch experiments the post-reaction mixture was filtered to remove the solids) or the liquid product (in continuous experiments the mesh closing the reaction channel prevented macroscopic removal of the catalyst) were collected in a round bottomed flask (20 mL). The samples were evaporated to remove organic compounds, dissolved in *Aqua Regia* and diluted with distilled water to a certain volume, and were then analysed by AAS (Perkin–Elmer).

3. Results and discussion

3.1. Catalyst characterisation

The porous structure characteristics of the carbon and the prepared Pd/C catalyst are reported in Table 1. The synthesised catalyst uses a new synthetic carbon support, specifically designed for deposition of metal nanoparticles with a controlled particle size distribution. The prepared Pd/C catalyst has a specific surface area of 727 m^2 g^{-1}, which is lower than that of the carbon support (1070 m^2 g^{-1}), that is, the support lost 32% of its area after impregnation of the palladium. It might be that the surface area loss is due to the pore blocking by the palladium nanoparticles. The XRD spectra showed the characteristic bands of the palladium phase for the prepared Pd/C catalyst and the calculated average particle size was *ca.* 4.8 nm. Such nanoparticles can easily block micropores of activated carbon support, which are in the range of *ca.* 1 nm diameter [12] and therefore reduce the area of the catalyst substantially.

Table 1
The porous structure characteristics of the carbon support and the prepared Pd/C catalyst.

	S_{BET} (m^2 g^{-1})	d (nm)	V_p (cm^3 g^{-1})
Carbon support	1070	13.3	0.195
Pd/C (5 wt%)	727	10.2	0.111

3.2. Evaluation of the catalytic reactivity for Heck C–C coupling reaction

In order to test the activity and selectivity of the prepared 5 wt% palladium on the carbon catalyst (Pd/C) in the Heck reaction, batch experiments were performed initially. For comparison purposes, a commercial palladium on an activated carbon catalyst (5 wt%, obtained from Sigma–Aldrich) was employed as well. The results of the batch Heck reaction (Table 2) show that the two catalysts have a similar performance in terms of selectivity to the main Heck coupling product (**3**). However, the reaction catalysed by the commercial catalyst achieved a 97% of substrate (**1**) conversion and a 81% yield of product (**3**) in 4.5 h, which were higher than that for the synthesised Pd/C catalyst (Table 2 and Fig. 2). The higher reaction kinetics of the commercial Pd/C catalyst may be attributed to its smaller size and therefore it's smaller contribution to intraparticle diffusion.

According to the mechanism of C–C coupling reactions using aryl iodides as reactants and catalysed by supported Pd catalysts, Pd(0) metal particles on the supports are in fact only precursors for the soluble palladium species that are the real catalysts in this system [12–17]. The activated carbon support of the commercial

Table 2
Results of batch Heck reaction[a] performed using Pd/C (5 wt%) catalysts.

Catalysts	Conversion of (**1**) (%)	Yield of (**3**)[b]	Selectivity to (**3**) (%)	Pd leaching (ppm)[c]
Pd/C, Sigma	97	81	85	11
Pd/C, this work	87	74	85	6

[a] Temperature (T) = 413 K, reaction time (t_R = 4.5 h, in dimethylformamide (DMF), triethylamine (TEA) as base.
[b] No *cis*-stilbene (**4**) was found in the product.
[c] Aqueous solution was prepared immediately after the reaction.

catalyst is in the form of a fine powder with the mean particle size of 20 μm which might make it much easier to release Pd nanoparticles into the reaction mixture as compared with the Pd/C where *ca.* 150 μm particles were used as the support. This hypothesis was confirmed by measuring the Pd content in the reaction solutions after the reactions. The Pd concentration was measured by atomic absorption in the cold or hot filtrates once the reaction period was completed.

Palladium (11 ppm) was measured in the filtrate of the commercial catalyst, which corresponded to 10% Pd leaching in respect to the initial loading of Pd onto the activated carbon. This was found to be greater than the corresponding value of the Pd/C catalysts synthesised in this work (6 ppm, corresponding to 6% Pd leaching). Because of the mechanism of the Pd-catalysed Heck reaction [13–15], which appears to require the presence of leached Pd, it is questionable whether a continuous Heck reaction is a feasible option. However, palladium should re-deposit on the surface of a support after the completion of the reaction due to: (i) the absence of aryl halides for oxidative addition, *i.e.* the absence of driving force for Pd to leave the support and (ii) the instability of the soluble Pd complexes. The solubilization/redeposition process was also found to be controllable by adjusting the reaction conditions [13–16]. Thus, Pd recovery might be achievable under flow conditions by using a bed of "empty" support (which could be subsequently used as an additional catalyst bed) following the bed of a supported Pd catalyst or by using an additional metal scavenger module [16].

3.3. Compact reactor performance in Heck C–C coupling reaction

The continuous Heck coupling reaction was conducted in a packed-bed compact reactor. In these experiments only the catalyst synthesised in this work was used; the Sigma Pd/C catalyst, due to small size of the particles, generated a high pressure drop across the reactor. Fig. 3 shows the reactor performances (as yield and selectivity) for the Heck coupling reaction as a function of the liquid feed rate. A clear dependence of the coupling products yield on the liquid flow rate was found in this study. For the very first continuous Heck coupling experiment with a fresh catalyst, the yield of 58% to coupling products (66% conversion of (**1**)) was measured at the flow rate of 0.25 mL min^{-1}, whereas, only 18% yield (20% conversion of **1**) was obtained for the flow rate of 2 mL min^{-1}. The variation of the residence time of liquid substrates in the reaction channels is due to the change of flow rate (calculated residence time of the liquid substrates in the reaction channels reduces from *ca.* 3 min to *ca.* 0.5 min by increase flow rate from 0.25 to 2 mL min^{-1}). The decrease in the residence time is the only explanation for the observed results, since the Heck coupling reactions are usually quite "slow" under batch conditions.

The selectivity to coupling products ((**3**) and (**4**)) in the continuous mode was found to be slightly higher than in the batch one (89% for the flow reactor *versus* 85% for the batch reactor). This can be attributed to the presence of *cis*-stilbene (**4**) in the product stream, which was confirmed by GC analysis. In the batch experiments, however, *trans*-stilbene (**3**) was the only Heck coupling product detected. It seems that the conditions of the continuous reactor with different mass and heat transfer characteristics compared to those of the batch reactor promoted the synthesis of *cis*-stilbene (**4**). However, the ratio of *cis* to *trans* product was very low and equal to *ca.* 1:40.

The higher conversions in the continuous reactor compared to those in the batch one (*e.g.* 58% of conversion for the residence time $t = 2.88$ min in the continuous reactor (Fig. 4) compared to *ca.* 150 min necessary for the same conversion in the batch reactor (see Fig. 3)) resulted in a much higher catalyst loading in the continuous reactor (500 mg of catalyst per cm^3 of the channel volume compared to 2.2 mg of catalyst per cm^3 of organic phase in the batch reactor).

Significant catalyst deactivation was found in the subsequent experiments, with yields dropping by *ca.* 60% for 0.25, 0.5 and 1 mL min^{-1} liquid flow rates, and by *ca.* 53% for the 1.5, and 2 mL min^{-1} flow rates. This is related to the reaction mechanism since Pd must be leached from the support and thus is no longer available for consecutive catalytic runs. Pd was detected at different levels in the products collected from continuous experiments.

3.4. Compact reactor performance in alkene hydrogenation

The Pd/C catalysed hydrogenation of intermediates (**3**) to the final product (**5**) (see the reaction scheme in Fig. 5) was performed continuously in the compact reactor to test the catalytic activity of the flow system for alkene hydrogenation. Fig. 5 shows the mo-

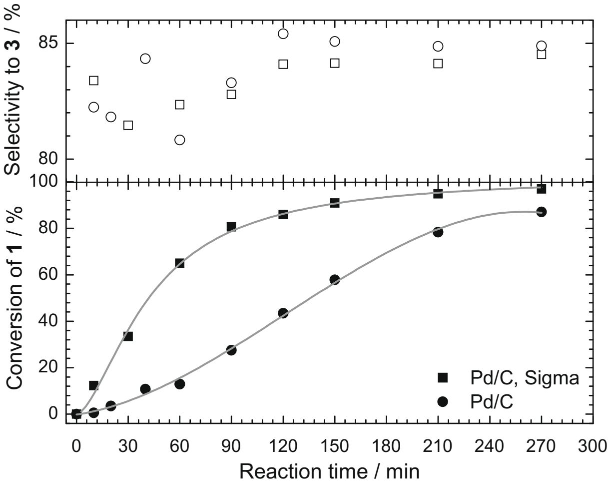

Fig. 3. Batch Heck C–C coupling reaction catalysed by supported palladium catalysts. Reaction conditions: 8 mmol of (**1**), 12 mmol of (**2**), 10 mmol of TEA and 0.1 mol% Pd in 8 mL of DMF, $T = 413$ K, under N_2.

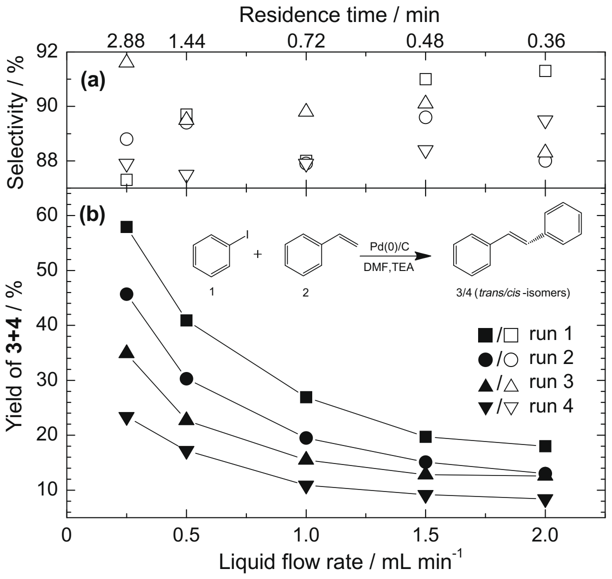

Fig. 4. Continuous Heck coupling reaction in the compact reactor. (a) Selectivity to **3** + **4**, (b) yield of **3** + **4**. Reaction conditions: $C_{1,0} = 0.5$ mol L^{-1}, $C_{2,0} = 0.75$ mol L^{-1}, $C_{\text{TEA},0} = 0.6$ mol L^{-1}, DMF as solvent, $T = 390$ K, two channels in series, approx. 0.9 g catalyst.

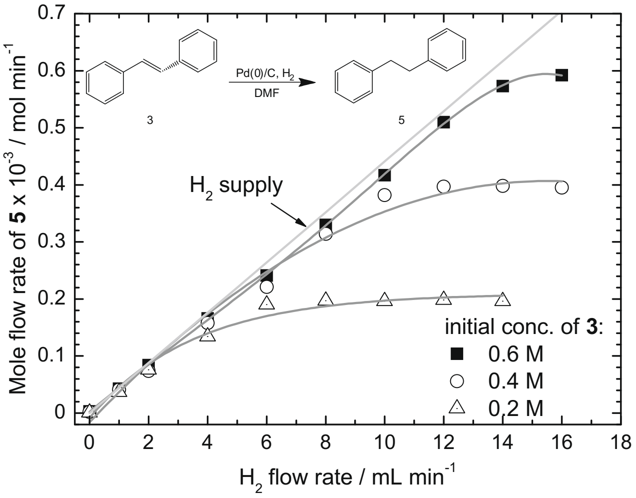

Fig. 5. Continuous alkene hydrogenation in the compact reactor. Reaction conditions: $T = 397$ K, $P = 8$ bar, $F_{\text{liquid}} = 1$ mL min^{-1}, two channels in series, approx. 0.9 g catalyst in the two channels.

lar flow rate of 1,2-diphenylethane (**5**) in the outlet of the reactor (measured at steady state) as a function of H_2 flow rate for the three initial substrate concentrations.

The Pd/C catalyst showed remarkable activity in the packed bed continuous-flow system. Furthermore, the yields of product (**5**) were found to correlate very well with the theoretical hydrogen supply to the system. This indicates that efficient gas/liquid mixing (mass transfer) was achieved by the integral static mixer within the reactor structure. Compared with the previous literature that used a batch reactor [17], the continuous flow packed-bed flow reactor enables a more efficient overall hydrogenation process: a lower temperature (398 K *versus* 413 K), a lower pressure (8 bar *versus* 20 bar) and a much shorter reaction time (*ca.* 6 min to achieve steady state with *ca.* 100% conversion *versus* 20 h reaction time).

3.5. Consecutive synthesis of 1,2-diphenylethane in a compact reactor

To evaluate the feasibility of consecutive Heck coupling and hydrogenation reactions under flow conditions, the reaction of 1,2-diphenylethane synthesis in four consecutively connected channels of the compact reactor was studied. The results are shown in Table 3. Compared with alkene hydrogenation, the Heck coupling reaction is the slower step of the two. A liquid flow rate of 0.25 mL min^{-1}, therefore, was used in the consecutive synthesis experiments in order to promote Heck coupling reaction.

The catalytic system was not found to be effective for producing the main desirable product (**5**) by using hydrogen to pressurise the system (Runs 1–3). Benzene (dehalogenation product of substrate (**1**)) and ethylbenzene (hydrogenation product of substrate (**2**)) were detected in the final product. This result indicates that the H_2 might back-flush into the Heck reaction channel and the Heck coupling reaction was suppressed due to the absence of substrates caused by their consumption in the side reactions. This hypothesis was supported by the measured significant increase in the amount of benzene with the increase of system pressure, *i.e.* H_2 pressure (Table 3, condition b). In order to eliminate the effect of side reactions, nitrogen was used to pressurise the whole system instead of hydrogen. After pressurising the system, a small stream of nitrogen (1 mL min^{-1}) was kept to flow through the reaction channels for providing an inert atmosphere for the Heck reaction. Then, a hydrogen stream was introduced into the hydrogenation channels. The system became more efficient for synthesising the target product. The complete conversion of the substrate (**1**) was achieved and a significant increase in the product yield (*ca.* 80% selectivity to final product) was measured (Runs 4 and 5). This result suggested that a stepwise conversion of the substrates/intermediate occurred in the continuous process. Compared with the system under condition (b) the target product yield became less dependent on the total pressure for condition (c). The same level of product yield can be achieved using moderate total pressure. High pressure is not essential for achieving high product yield.

One disadvantage of the present system is the use of DMF as a solvent which is toxic and difficult to evaporate during the following workup. Therefore, finding a suitable substitute to replace DMF is essential to make the whole system more environmentally benign. Ethanol is innocuous and less expensive and was considered in this study. Furthermore, due to the flow reactor being pressurised, solvents with lower boiling points can be held in reaction channels as superheated liquids to promote the reaction. In our experiments (Table 3 condition d), ethanol was used as a solvent for the hydrogenation reaction, Scheme 1, at 393 K and elevated pressure under continuous flow (Runs 6 and 7). The process with ethanol was as effective and efficient as the one using DMF, *i.e.* the same level of substrate conversion and yield of product (**5**) were obtained.

3.6. Retention of Pd in a flow reactor

The aforementioned solubilization/redeposition was well studied and supported by several batch investigations [13–16,18]. Even in a flow reactor [19], this mechanism was employed as well for retrieving leached species from the continuous Heck reactions (by inserting a column containing the metal scavenger resin after

Table 3
Optimization of the flow chemistry[a] in the compact reactor for a desirable multi-step organic synthesis (Scheme 1).

Run	Pressure (bar)	Solvent	PhI conversion (%)	Selectivity (%)		
				trans/*cis*-Stilbene (**3**/**4**) intermediate	1,2-Diphenylethane (**5**) product	Benzene by-product[e]
1	1[b]	DMF	83	38	38	23
2	4[b]	DMF	96	0	18	81
3	8[b]	DMF	100	0	5	95
4	4[c]	DMF	99	1	80	15
5	8[c]	DMF	100	0	82	13
6	4[d]	EtOH	100	0	83	13
7	8[d]	EtOH	100	0	83	12

[a] Reaction conditions: $C_{1,0} = 0.4$ mol L^{-1}, $T = 393$ K, $F_{\text{liquid}} = 0.25$ mL min^{-1}, $F_{\text{hydrogen}} = 8$ mL min^{-1}, four channels in series, approx. 0.9 g catalyst for the Heck reaction, approx. 0.75 g catalyst for the alkene hydrogenation.
[b] System was pressurised with H_2.
[c] System was pressurised with N_2.
[d] System was pressurised with N_2, ethanol was used as solvent.
[e] Analysis of the reaction did not include the production of ethylbenzene due to the excess of styrene in the system.

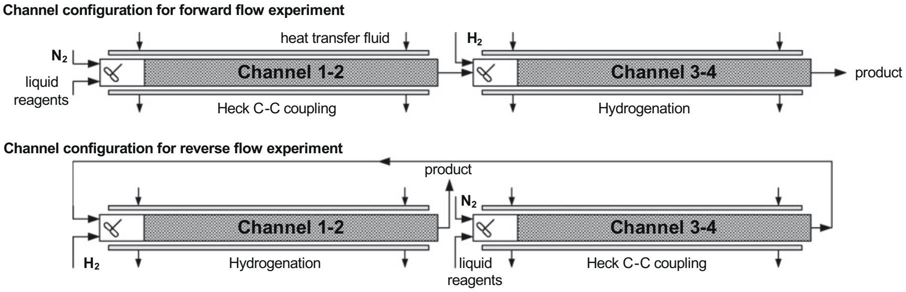

Fig. 6. Channel configurations for normal/reverse flow experiments.

the reaction column). In the present flow reactor, the subsequent hydrogenation channels can actually serve as scavengers to recapture the leached Pd species from the Heck reaction channels. Theoretically, the catalytic activity of the system could be maintained for both the reactions by reverse running [20,21] the two reactions in each other's channels under carefully chosen conditions. The channel arrangement for this concept is shown in Fig. 6. This hypothesis was proved by the experimental results in Fig. 7 (only one set of results from forward/reverse runs is presented in Fig. 7, the same reaction profiles as for reverse run were obtained in two consecutive experiments). The reuse of the catalyst is viable without major deactivation by obverse/reverse running two reactions in each other's reaction channels. Most of the leached Pd species were found to re-deposit on the support during hydrogenation under the conditions used in this study, which was proven by XPS analysis. Compared with the fresh catalyst in Channel 4, Pd species on the carbon surface were found to have increased by 79% (from 1.4% to 2.5%) after one experiment. Accordingly, a decrease of oxygen on the carbon surface from 26.2% to 22.3% was measured which indicates the consumption of oxygen containing surface groups by redeposition of Pd in hydrogenation channel. Zhao et al. [13–15] and Heidenreich et al. [16] confirmed this reversible transfer of Pd species between solvent and support in their studies and asserted that a unique process is tuneable by carefully choosing reaction conditions and base.

One consequence of using triethylamine as a base in this flow reaction system is the formation of triethylammonium hydrohalide salts. These are formed by reaction of the amine with the hydrogen halide, which is released during C–C coupling. It has been reported that in heterogeneous systems the formation of triethylammonium hydrohalides might have detrimental effects on catalyst activity [13,22]. This is due to adsorption of the halide salts on the catalyst surface, which subsequently prevents redeposition of Pd from solution to the catalyst. Zhao *et al.* [13] asserted that adsorption of the triethylammonium iodide on the support is one of the reasons for hindering Pd redeposition; a batch reactor with Pd-supported catalysts in a *N*-methylpyrrolidone (NMP) solvent was used. However, in the current study, the presence of triethylammonium iodide species was not determined. With regard to the flow system used here (with either DMF or ethanol as solvent), the influence of the dissolved triethylammonium hydrohalides on catalyst deactivation deserves further study. Note that triethylammonium hydrohalides are known to be soluble in polar solvents; especially in aprotic polar solvents such as NMP, DMF and 1,4-dioxane [22]. Thus, in the reaction in a polar solvent used in this study the deposition of salt may have been prevented. Additionally further investigation is needed to optimise the present catalytic system in order to minimise the loss of Pd from the reactor, and to promote rapid redeposition of the Pd species onto the support.

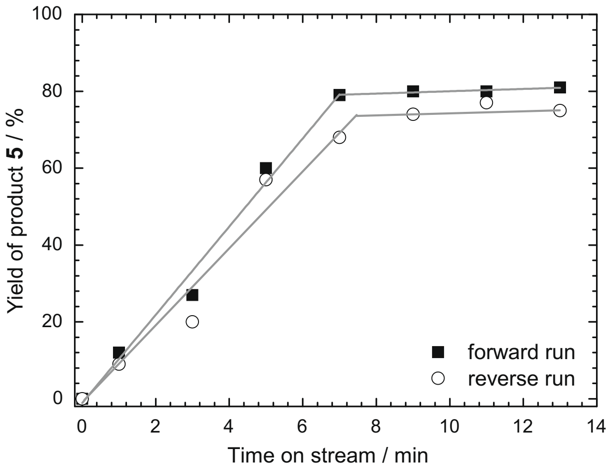

Fig. 7. Time yield of 1,2-diphenylethane **5** for the normal flow direction and the reverse flow direction runs. Reaction conditions: $C_{1,0} = 0.4\ \mathrm{mol\ L^{-1}}$, $T = 393$ K, $P = 4$ bar, $F_{\mathrm{liquid}} = 0.20\ \mathrm{mL\ min^{-1}}$, $F_{\mathrm{hydrogen}} = 8\ \mathrm{mL\ min^{-1}}$, EtOH as solvent, four channels in series, approx. 0.9 g catalyst for Heck reaction, approx. 0.75 g catalyst for the alkene hydrogenation.

4. Conclusions

The suitability of a compact multichannel reactor for multi-step organic synthesis was investigated using a conventional 'one-pot' reaction, *i.e.* a Heck C–C coupling reaction followed by hydrogenation for synthesising 1,2-diphenylethane. Compared with conventional batch reactors, the compact reactor promoted a more intensified Heck reaction and alkene hydrogenation. 1,2-Diphenylethane was synthesised using the flow compact reactor within minutes of residence time with a lower operating temperature and pressure. In comparison, the conventional batch synthesis took several hours for a similar yield. A stepwise conversion of the substrates to the final product was achieved in the compact multichannel reactor by coupling the Heck reaction and hydrogenation. Compared with the batch reactor, this flow chemistry process in the compact reactor features some advantages such as: (i) being more intensified (much shorter residence time) due to the high catalyst/substrates ratio, (ii) being operated under benign conditions, *i.e.* lower temperature and pressure, (iii) using superheated ethanol at elevated pressure which makes the process greener.

Leached Pd species were believed to be active for igniting and promoting the Heck reaction. Due to (i) the reversible transfer mechanism of Pd species between solvent and support, and (ii) the unique mass transfer of Pd in different reaction channels, catalytic activity of the system can be mostly maintained by reverse running the two reactions in one another's reaction channels. This continuous catalytic system might be a promising alternative to replacing the conventional batch reactor for multi-step synthesis.

The present investigation demonstrated that a compact reactor is capable of performing the multi-step synthesis in one stream. Considering the specific reaction used in this study, *i.e.* C–C coupling reactions, however, there is still much room left for optimising this flow catalytic system with compact reactor. Therefore, future studies on C–C coupling reactions in this flow reactor system are suggested to focus on (i) developing the ligand-free catalytic system which is capable of effectively and efficiently catalysing C–C coupling reactions involving aryl bromides and aryl chlorides (less active, more practical and economical substrates), (ii) minimising the Pd leaching by either optimising present flow catalytic system or engineering new supported Pd catalysts for true surface catalysis. The optimisation of styrene concentration is also necessary to reduce the formation of by-products (ethylbenzene).

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