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Flow Chemistry Syntheses of Styrenes, Unsymmetrical **Stilbenes and Branched Aldehydes**

Samuel L. Bourne,^[a] Matthew O'Brien,^[b] Sivarajan Kasinathan,^[c] Peter Koos,^[a] Päivi Tolstoy,^[a] Dennis X. Hu,^[a] Roderick W. Bates,^[c] Benjamin Martin,^[d] Berthold Schenkel,^[d] and Steven V. Lev*^[a]

Two tandem flow chemistry processes have been developed. A single palladium-catalysed Heck reaction with ethylene gas provides an efficient synthesis for functionalised styrenes. Through further elaboration the catalyst becomes multi-functional and performs a second Heck reaction providing a single continuous process for the synthesis of unsymmetrical stilbenes. In addition, the continuous, rhodium-catalysed, hydroformylation of styrene derivatives with syngas affords

Introduction

Over the last few years, continuous flow chemistry and the use of microreactors^[1] in the research environment has evolved as an enabling technology for organic synthesis programs. Since chemists in both academia and industry are seeking to create more sustainable and environmentally acceptable approaches to their work,^[2] flow chemistry can provide an attractive option. The advent of new functional materials continually provides synthesis chemists with exciting new opportunities to compare the attributes of traditional batch mode methods of molecular assembly with continuous telescoped flow processes, especially in terms of safety, efficiency, low solvent usage and energy consumption.

Recent examples of the use of flow devices demonstrate their further ability to safely contain hazardous reagents^[3] and optimise chemical processes, even under pressurised and

- [a] S. L. Bourne, Dr. P. Koos, Dr. P. Tolstoy, D. X. Hu, Prof. S. V. Ley Department of Chemistry University of Cambridae Lensfield Road, Cambridge, CB2 1EW (UK) E-mail: svl1000@cam.ac.uk
- [b] Dr. M. O'Brien School of Physical & Geographical Sciences Lennard-Jones Building, Keele University Staffordshire, ST5 5BG (United Kingdom)
- [c] S. Kasinathan, Dr. R. W. Bates Division of Chemistry and Biological Chemistry School of Physical and Mathematical Sciences Nanyang Technological University 21 Nanyang Link, 637371 Singapore (Singapore)
- [d] Dr. B. Martin, Dr. B. Schenkel Chemical & Analytical Development Novartis Pharma AG, Werk Klybeck Klybeckstr. 141, 4057 Basel (Switzerland)

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branched aldehydes with good selectivity. Incorporation of an in-line aqueous wash and liquid-liquid separation allowed for the ethylene Heck reaction to be telescoped into the hydroformylation step such that a single flow synthesis of branched aldehydes directly from aryl iodides was achieved. The tube-intube semi-permeable membrane-based gas reactor and liquidliquid separator both play an essential role in enabling these telescoped flow processes.

super-heated conditions. The use of low temperature devices^[4] and the ability to pump slurries and particulates^[5] is also becoming part of the standard repertoire of flow chemistry equipment. Additionally, the ability to readily scale-up through scaling-out with multiple reactors or with extended run times is now common practice in the area.

In a similar way, the containment of reactive gases at elevated or ambient pressure can easily be achieved in flow, for example, the invention of semi-permeable membrane-based devices, which facilitate the rapid continuous generation of homogeneous solutions of gas. Many of the safety concerns surrounding the use of toxic or flammable gases in batch mode, such as uncontrolled depressurisation and reactor head-space volume, can be mitigated by moving into flow mode. There are several advantages of using gaseous reagents in synthesis chemistry. Not only are many synthetically useful gases readily available and relatively inexpensive but these reagents can easily be used in excess to drive reactions to completion as work-up and purification simply involves controlled depressurisation and venting.

To exploit these possibilities, we conceived of gas-liquid flow reactors based on the semi-permeable amorphous fluoropolymer Teflon AF 2400^[6] (Figure 1). We have successfully used these reactors to introduce gases such as CO₂, ^[7a] CO, ^[7b] O₂, ^[7c] $O_{3^{\prime}}{}^{[7d]}$ $H_{2^{\prime}}{}^{[7e,f]}$ $NH_{3}{}^{[7g,h]}$ and $C_{2}H_{4}{}^{[7i]}$ into reaction streams.

In this paper we will give a full account of our work with ethylene and syngas^[7]] (CO/H₂ 1:1) for carbon-carbon bondforming processes during the syntheses of styrenes and branched aldehydes, respectively (Scheme 1). Furthermore, we will describe how we were able to telescope these two processes into a continuous tandem sequence with the incorporation of a continuous liquid-liquid separation system recently developed in our laboratories.





Figure 1. The semi-permeable membrane-based tube-in-tube gas reactor. The primary manifold is constructed from commercially available Swagelok fittings. The outer tube is standard PTFE tubing (wall thickness = 1 mm) and the inner tubing AF 2400. o.d. = Outer diameter; i.d. = internal diameter.



Scheme 1. The palladium-catalysed cross-coupling reaction of aryl iodides with ethylene gas to afford functionalised styrenes, followed by a rhodium-catalysed hydroformylation or a second Heck reaction to afford branched al-dehydes or unsymmetrical stilbenes, respectively.

Following on from the initial pioneering work of Mizoroki^[8] and Heck,^[9a,b] there has been a profusion of literature reporting this popular palladium-catalysed cross-coupling of aryl halides with common olefins, including some flow syntheses.^[10] Indeed, the reaction has become an important component in the toolbox of the synthesis chemist. Nevertheless, the vinylation of aryl halides is less straightforward, often involving the use of vinyl surrogates such as potassium vinyltrifluoroborate or vinyltributyltin installed through the palladium-catalysed Suzuki^[11] or Stille^[12] cross-coupling methodologies, respectively. However, there are associated drawbacks to these reactions, namely, toxicity, expense, difficult work-up procedures and significant amounts of waste. Ethylene has also been used as a reagent in the synthesis of styrenes^[13] since its use in early examples of the Heck reaction, which typically require high pressures of ethylene to prevent the formation of stilbenes.^[9] Examples in the literature that use low pressures of ethylene typically employ more stable palladacycles as catalysts,^[14] as opposed to traditional palladium salts, which allow greater control of selectivity. Providing the initial styrene products of an ethylene Heck process are of high enough purity, it is conceivable that, after depressurisation and venting of excess ethylene, a second aryl halide be introduced to afford unsymmetrical stilbene products^[15] via a further cross-coupling. Leadbeater et al.^[13a] have reported a one-pot, two-step microwave approach to the synthesis of unsymmetrical stilbenes by using ethylene, whereby a second portion of palladium catalyst with the second coupling partner is added after the initial vinylation step. However, more reactive aryl iodides have been reported to form symmetrical stilbenes leading to complex mixtures in the second coupling step. Good to excellent conversions were reported but isolated yields were poor owing to the isolation from DMF.

Hydroformylation is another atom-efficient carbon–carbon bond-forming method,^[16] whereby single molecules of CO and H₂ are added across an olefinic bond to afford synthetically versatile aldehyde products. The hydroformylations of aromatic alkenes and vinyl ethers tend to afford the branched regioisomer,^[17] whereas for many industrial applications^[18] of hydroformylation, linear aldehydes are the major product of aliphatic alkenes.^[19] The more structurally interesting branched isomer is less straightforward to prepare on an industrial scale as it often requires poorly efficient processes. Varying the electronic nature of substituents attached to the alkene can strongly influence the selectivity of the reaction, whereas the catalyst and the ligand system play a dominant role in determining the regioselective outcome of the reaction.

We envisaged that the telescoping of the flow chemical synthesis of styrenes into a hydroformylation reaction to afford branched aldehydes directly from the corresponding aryl iodides would represent an attractive sequence, whereby two new C-C bonds would be formed. This process was studied earlier by M. Arai et al.^[13c] who showed that a bifunctional catalytic system containing homogeneous Rh(CO)₂(acac), PdCl₂ and Ph₃P gave high conversion if used in two separate environments. However, if combined, the hydroformylation is hindered significantly by the presence of palladium, whereas the yield of the first Heck reaction is unaffected. We considered that palladium metal could interfere in the hydroformylation cycle with a fully telescoped process and therefore potential reaction incompatibility is a major consideration on attempting to telescope reactions in a continuous fashion. Our group, however, has recently focused on enabling technologies to address these downstream processing issues and, in particular, the use of in-line liquid-liquid separation^[20] as a potential solution to the problem.

Results and Discussion

We began by investigating the Heck reaction of 3-iodoanisole with ethylene gas by using the gas-flow apparatus setup shown in Scheme 2. lodide **1a** (0.5 mmol), triethylamine (2 equiv.), additive (1 equiv.) and the catalyst (5 mol%) were dissolved in solvent (5 mL) and loaded into a 5 mL polyether–ether–ketone (PEEK) sample loop. A Uniqsis FlowSyn reactor was used to pump the reagents at 1 mLmin⁻¹ through the tube-in-tube gas reactor pressurised with ethylene at 15 bar (1 bar = 100 kPa). The reaction stream was then passed through a 20 mL polymeric perfluoroalkoxy (PFA) reaction coil maintained at a temperature of 120 °C, after which the reaction



Scheme 2. The gas-flow reactor configuration for optimisation of the Heck cross-coupling between ethylene and aryl iodide 1 a.

stream passed through a 20 bar back-pressure regulator (BPR). This was required to maintain a homogeneous solution by preventing out-gassing.

The initial optimisation reactions were concerned primarily with Pd black formation, which we anticipated would cause fouling or blockage problems that must be avoided in flow chemistry systems. Previous work on carbonylation reactions^[7b] in flow has shown that the use of palladium XantPhos complex in dioxane as solvent suppressed the formation of this undesired precipitant. Although the XantPhos ligand is not commonly the ligand of choice for Heck reactions, it enabled rapid initial optimisation without any complications. Shown in Table 1 are the results obtained by varying reaction time, temperature and ethylene pressure.

The initial set of conditions (entry 1, Table 1) afforded a low 27% conversion to the desired product. Varying the reaction temperature showed some improvement to 36% conversion at 120°C. However, increasing the temperature still led to decomposition. Furthermore, a screen of ethylene pressure revealed that higher pressures improved the conversion and that increasing the reaction time to beyond 50 min led to no improvement. The best conditions from these optimisation studies were then used to screen a range of alternative ligands (Table 2).

Table 1. Initial optimisation with 3-iodoanisole. ^[a]					
Entry	<i>T</i> [°C]	t [min]	C ₂ H ₄ [bar]	Conv. ^[b] [%]	
1	100	50	15	27	
2	80	50	15	13	
3	120	50	15	36	
4 ^[c]	140	50	15	-	
5	120	20	15	15	
6	120	30	15	12	
7	120	50	15	36	
8	120	70	15	31	
9	120	50	2	22	
10	120	50	5	24	
11	120	50	10	32	
12	120	50	15	36	
13 ^[d]	120	50	15	32	
14 ^[e]	120	50	15	10	
[a] Substrate (0.5 mmol), dioxane (0.1 M), Pd(OAc) ₂ (5 mol%), XantPhos (6 mol%), Et ₃ N (2 equiv.). [b] Conversions determined by ¹ H NMR analysis.					

(6 mol %), Et₃N (2 equiv.). [b] Conversions determined by 'H NMR analysis.
 [c] Primarily decomposition observed. [d] EtN(*i*Pr)₂ was used as base.
 [e] DBU was used as base.

Table 2. Screening of various ligands. ^[a]					
Entry	Ligand	[mol%]	Conv. ^[b] [%]		
1	XantPhos	6	36		
2	JohnPhos	12	46		
3	SPhos	12	5		
4	XPhos	12	10		
5	tBu₃P•HBF₄	15	25		
6 ^[c]	Ph₃P	15	-		
[a] Et_3N (2 equiv.), Pd(OAc) ₂ (5 mol%), dioxane (0.1 M), $T=120$ °C, $t=50$ min, ethylene ($P=15$ bar). [b] Determined by ¹ H NMR analysis. [c] Starting material recovered.					

Although the monodentate ligands tBu_3P and Ph_3P also inhibited the formation of precipitates, their use was accompanied with very low conversions (entries 5–6, Table 2). The XPhos and SPhos ligands^[21] also led to low conversions. The JohnPhos ligand, however, led to a 46% conversion but, unfortunately, this ligand also resulted in the formation of minor amounts of Pd black precipitate. Encouraged by literature reports, we then investigated the use of tetraalkylammonium salts as additives.^[22] The use of a solvent mixture containing DMF was necessary for these reactions to keep all components in solution.

Interestingly, a significant improvement (from 46% to 54%) was achieved simply by the addition of DMF as co-solvent (entry 1, Table 3). Tetrabutylammonium iodide (TBAI) led to a much more dramatic improvement, affording a 94% yield if added in 100 mol%. Both tetrabutylammonium acetate and tetrabutylammonium chloride led to improvements over the control reaction with no additive but these improvements were more modest (entries 3 and 7, Table 3). It was found that the addition of sub-stoichiometric amounts of TBAI actually led to a drop in conversion compared with the control reaction, indicating that the mode of influence of this additive on the reaction pathway was not straightforward. In these reactions that use the JohnPhos ligand, some Pd black precipitate was clearly observed. To filter this inline, a small cartridge packed with cotton wool was placed just upstream of the back pressure regulator at the end of the system.

Table 3. Screening of various additives. ^[a]				
Entry	Et₃N [equiv.]	Additive	[equiv.]	Conv. ^[b] [%]
1	2	-		54
2	0	<i>n</i> Bu₄NOAc	2	70
3	2	<i>n</i> Bu₄NOAc	1	60
4	2	<i>n</i> Bu₄NOAc	2	84
5	2	TBAI	1	94
6	2	TBAB	1	86
7	2	TBACI	1	66
8	2	TBAI	0.5	44
9	2	TBAI	0.2	28
10 ^[c]	2	TBAI	1	96
[a] Substrate (0.5 mmol), $Pd(OAc)_2$ (5 mol%), JohnPhos (12 mol%), DMF/ dioxane (1:4), $T = 120$ °C, $t = 50$ min, ethylene ($P = 15$ bar). [b] Determined by ¹ H NMR analysis. [c] A residence time of 20 min was used.				

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The rapid change in colour from pale orange to a clear solution in the first section of the reactor coil suggested that, with this new catalyst-additive system, the reaction was taking place at a much higher rate. This was confirmed when essentially identical conversions were obtained on decreasing the reaction time to 20 min (flow rate = 1 mLmin⁻¹, 20 mL coil). At this stage, given that the DMF co-solvent had displayed a significant improvement in conversion, we decided to rescreen some of the alternative main solvents, from which toluene was identified as an improved option. Although the non-coordinating nature of toluene is known to limit ligand displacement from the palladium centre,^[23] the DMF co-solvent seemed to override this effect and a toluene/DMF (4:1) mixture provided the desired solubility and resulted in higher conversions for the majority of substrates. With this solvent mixture and catalyst-additive system, we investigated the preparative formation of a series of styrene derivatives.

The Heck coupling of ethylene with a series of aryl iodide substrates was performed to evaluate the scope of the reaction, the results of which are shown in Table 4. As can be seen, the reaction generally proceeded with good to excellent conversions and the products were mostly isolated in high yield. Both electron rich and electron deficient iodides were tolerated. All of the styrene products were purified by distillation leading to a lower yield (typically 10-15% lower), presumably owing to mechanical losses on this relatively small scale (0.5 mmol). Both benzylic and phenolic hydroxyl substituents were well tolerated (entries 7-9, Table 4). The only substrate that gave a poor isolated yield of product was the *p*-nitro substituent 6a. In this case the conversion was only a low 60% with remaining starting material. As will be shown below, this result was significantly improved upon with additional optimisation. No stilbene formation was observed whatsoever. Having established that the process was generally applicable to the vinylation of aryl iodides, we also briefly investigated its extension to aryl bromides and some heteroaromatic iodides, the results of which are shown in Table 5.

Low conversion of the aryl bromides to the desired styrenes was not unexpected given that bromides are, in general, less reactive than iodides in this type of reaction. The heteroaryl iodide substrates **13a** and **14a** gave no reaction at all. However, it is known that the palladium complex intermediates with these 2-substituted substrates are prone to dimerisation, thereby poisoning the catalyst and reducing catalyst turnover numbers.^[24] lodide **15a** afforded the most promising result for heteroaromatic systems, with a conversion of 46% and isolated yield of 40%. The reaction was clean with only starting material remaining.

At this stage of the investigation we considered optimising the process for aryl bromides. However, since concurrent investigations in our laboratory involving hydroformylation were progressing well, we chose to focus on scaling-up the styrene synthesis in preparation for telescoping the two transformations.

To achieve scalable reaction conditions, especially in the context of tandem flow processes, it was of primary importance to prevent the formation of Pd black entirely. We re-in-



[a] Aryl iodide (0.5 mmol), Et₃N (2 equiv.), Pd(OAc)₂ (5 mol%), JohnPhos (12 mol%), TBAI (1 equiv.), DMF/PhMe (1:4), T = 120 °C, t = 20 min, flow rate = 1 mLmin⁻¹, ethylene (P = 15 bar), AF 2400 (l = 0.7 m). [b] Isolated yields after distillation.

vestigated the tBu_3P and Ph_3P ligands that had shown good homogeneity in earlier experiments, despite leading to low yields. The highly electron rich tBu_3P ·HBF₄ ligand salt developed by G. Fu et al.^[25] gave an active homogeneous catalyst. Furthermore, Et₃N was substituted for Cy₂NMe, which has been shown to increase catalyst turnover^[24b] and this also led to improvements in our process. Somewhat surprisingly, the Heck coupling of aryl bromides with ethylene under these conditions still gave poor conversions despite the precedence for good conversions if using activated olefins such as acrylates. This was attributed to the very short reaction times we were implementing in flow.

With a procedure now free of Pd black formation the flow reaction was optimised for scale-up (Table 6). The catalyst loading and additive equivalencies were decreased and substrate concentration was increased to maximise the reaction throughput.

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Increasing the overall reaction concentration and substantially reducing both the catalyst (to 0.5 mol%) and additive (to 0.1 equiv.) loadings had no adverse effect on the reaction and high conversions were maintained (entries 1–5). Reducing the additive concentration was previously not possible with the JohnPhos ligand so this was a welcome surprise and a benefit to the reaction process. However, if the additive was completely removed the catalyst activity fell away dramatically (entry 7). Increasing the substrate concentration resulted, perhaps not surprisingly, in the formation of the symmetrical stilbene byproduct (entry 6) but this side reaction could be suppressed completely by using a substrate concentration of 0.5 m and by increasing the ethylene gas pressure in the gas reactor from 6 to 15 bar (entry 8). Preventing stilbene formation at 1 m substrate concentration was not possible because ethylene pres-

Table 6. Optimisation for scale-up. ^[a]					
Entry	Conc. [м]	TBAI [equiv.]	Catalyst [mol %]	Conv. styrene ^[b] [%]	Conv. stilbene ^[b] [%]
1	0.1	1.0	5.0	96	0
2	0.2	0.5	2.5	93	3
3	0.3	0.3	1.7	93	4
4	0.5	0.2	1.0	86	11
5 ^[c]	0.5	0.2	1.0	98	0
6 ^[c]	1.0	0.1	0.5	88	11
7 ^[c,d]	0.5	-	1.0	39	0
8 ^[c]	0.5	0.1	0.5	99	0
[a] 4-ioo (1.2 equ	[a] 4-iodoanisole (X mmol), $Pd(OAc)_2$ catalyst, $tBu_3P HBF_4$, Cy_2NMe (1.2 equiv.), DMF/toluene (1:4), $T = 120 \degree C$, $t = 20 min$, ethylene ($P = 6$ bar) unless stated otherwise. [b] Percentage conversions based on ¹ H NMR				

analysis of crude product. [c] Ethylene (P = 15 bar). [d] No additive used.

sures approaching 20 bar were not sufficient and technical issues prevented higher pressures than this from being used. An additional problem arising from the higher 1 M substrate concentration was precipitation of Cy₂NMeH⁺I⁻ salt, which caused some blocking of the flow channel.

The conditions highlighted (entry 8, Table 6) were used for the scale-up reaction (Scheme 3). A premixed 0.5 M (28 g of iodide **5 a**, 240 mL) reaction solution was prepared and



Scheme 3. Flow setup for the scale-up process with 4-iodoanisole 5 a.

pumped continuously for 4 h without interruption.

In the scale-up run, the conversion decreased slightly to 92% and led to an overall isolated yield after distillation of 84% (13.5 g). Having observed significantly improved activities with this new catalyst system, we were encouraged to investigate its use with a further series of substrates, including some heteroaromatic iodides and the *p*-nitro compound **6a**, which had previously reacted poorly. These examples are shown in Table 7.

Pleasingly, the vinylation of aryl iodides with the new catalyst system and TBAI (0.1 equiv.) as additive led to excellent yields of the corresponding styrenes, which were generally isolated in very high yield. The reaction of pyridyl species **20a** and **21a** proceeded cleanly and gave high conversions, however, the corresponding styrene products were difficult to isolate owing to their volatility or propensity to decompose on silica gel. Notably, the *p*-nitro compound **6a**, which previously had reacted with 60% conversion (43% isolated yield) now provided the corresponding styrene **6b** in almost quantitative yield, thus highlighting the benefits that can be achieved by this progressive re-optimisation.

Following scale-up studies, we were pleased that sufficient ethylene was clearly permeating into the reaction stream through the Teflon AF 2400 semipermeable membrane. However, we sought to obtain a more quantitative picture of the situation. Based on previous successes within the group, we were confident that continuous flow IR spectroscopy would be of value. With the aid of an in-line ReactIR flow cell^[26] to measure the intensity of the asymmetrical CH₂ bend in ethylene at 952 cm⁻¹, it was possible to quantify the amount of ethylene in the solvent stream as a function of pressure and flow rate (Scheme 4).

Calibrating the IR data with gas burette measurements showed that a difference in absorption of 0.01 A.U. corresponded to a concentration difference of 1.48 mL (0.066 M) of ethylene gas per 1 mL of toluene. The graph in Figure 2a shows that the concentration of ethylene increases linearly



[a] Substrate (0.3 mmol), Cy₂NMe (1.2 equiv.), Pd(OAc)₂ (1 mol%), tBu_3P ·HBF₄ (2 mol%), TBAI (0.1 equiv.), MeOH/MePh (1:9), T = 130 °C, t = 20 min, flow rate = 1 mL min⁻¹, ethylene (P = 10 bar), AF 2400 (I = 0.7 m). [b] Isolated yield after distillation unless stated otherwise. [c] Volatile. [d] Insoluble. [e] Acid work-up not possible. [f] Purified by column chromatography.







Figure 2. a) Intensity of ethylene stretching frequency at 952 cm⁻¹ vs. pressure at a constant flow rate of 1.0 mL min⁻¹. b) Absorbance of ethylene vs. flow rate at constant pressure of 10 bar.

with increasing gas pressure at a given flow rate and residence time. However, in Figure 2b, the concentration also increases with decreasing flow rate, suggesting that the solvent stream does not reach ethylene saturation at the higher flow rates such as those used in the ethylene Heck reactions. The rate of gas permeation/ethylene flux over the membrane can be described by using Fick's law in this case. On using other gases, such as hydrogen, saturation of the solvent stream is achieved and, hence, it is more appropriate to use Henry's law to relate pressure with the amount of dissolved gas. However, both give an approximately linear progression.

Another advantage that flow chemistry often boasts over typical batch protocols is the ability to telescope reactions together, eliminating time consuming intermediate work-up and purification operations and protecting sensitive intermediates. Styrene products, which are particularly difficult to isolate owing to their volatility or reactivity (styrenes are quite prone to aerobic oxidative polymerisation), could be used directly in a second reaction process, thereby preventing losses resulting from evaporation or decomposition. We envisioned that a sequential double-Heck type reaction, which would only require a single addition of catalyst, might exploit this advantage to afford unsymmetrical stilbene products in high yield and purity (Scheme 5).



Scheme 5. Flow setup for the vinylation $Ar^{1}I$ followed by a second Heck reaction with $Ar^{2}I$ to afford unsymmetrical stilbenes.





[a] Conditions A: 1) Ar¹I (0.6 mmol), Cy₂NMe (2.2 equiv.), Pd(OAc) (1 mol%), tBu₃P·HBF₄ (2 mol%), TBAI (1 equiv.), DMF/PhMe (1:4), T= 120°C, t=20 min, flow rate = 1 mLmin⁻¹, ethylene (P=10 bar), AF 2400 (l=1.5 m); 2) Ar²I (0.6 mmol), DMF/PhMe (1:4), T=120 °C, t=50 min,pump A flow rate = 0.2 mLmin⁻¹, pump B flow rate = 0.2 mLmin⁻¹. Conditions B: 1) Ar¹I (0.6 mmol), Cy₂NMe (2.2 equiv.), Pd(OAc)₂ (1 mol%), tBu₃P·HBF₄ (2 mol%), MeOH/PhMe (1:9), T=130 °C, t=20 min, flow rate= 1 mLmin⁻¹, ethylene (P = 10 bar), AF 2400 (l = 1.5 m); 2) Ar²I (0.6 mmol), MeOH/PhMe (1:9), $T = 130 \degree$ C, t = 50 min, pump A flow rate = 0.2 mLmin⁻¹, pump B flow rate = 0.2 mLmin^{-1} . [b] Isolated yields after column chromatography; selectivities of trans-1,2-diaryl vs. 1,1-geminal product (t/g); conversions determined by ¹H NMR analysis of crude product. [c] ¹H NMR of crude product not analysed. [d] Product was insoluble and caused blocking. [e] No reaction was observed with 1-vinvlnapthaline. [f] 1,2diaryl. [g] 1,1-geminal products were both isolated. [h] A combined flow rate of 0.3 mLmin⁻¹ was used in step 2.

The results published in our initial communication demonstrated that the double Heck process was possible, but that the scope of the reaction was somewhat limited owing to the variable reactivity of certain styrene intermediates in the second Heck coupling.^[7]]

Two sets of reaction conditions were used-conditions A: Pd(OAc)₂, tBu₃P·HBF₄, Cy₂NMe (2.2 equiv.), TBAI (1 equiv.) and DMF/PhMe (1:4) solvent system; conditions B (optimised after finding that MeOH could be used as co-solvent): Pd(OAc)₂, tBu₃P·HBF₄, Cy₂NMe (2.2 equiv.) and MeOH/PhMe (1:9) solvent system. Concurrent investigations towards streamlining the ethylene Heck and the hydroformylation reactions into a single telescoped process to afford branched aldehydes directly from the aryl iodide starting materials found that MeOH was a more favourable co-solvent than DMF. Consequently, the use of an MeOH/PhMe (1:9) solvent system led to equivalent or better conversions to styrene and obviated the use of TBAI as an additive. Conditions B can be applied for all substrates to achieve good yields, with the exception of 1-vinylnaphthalene 19b (entry 14, Table 8), which showed no reactivity towards various aryl iodides. Conditions A worked well in the formation of strongly electron withdrawing olefins but showed reduced reactivity in the second coupling step in the formation of electron rich olefins.

For the 16 examples given, selectivities towards the 1,2diaryl versus the 1,1-geminal diaryl product vary between 85 and 100%. For stilbene **39** (entry 15, Table 8), both products were isolated by column chromatography and their respective yields reported.

As mentioned above, previous investigations were directed towards the synthesis of branched aldehydes by the hydroformylation of functionalised styrene starting materials. To demonstrate the potential of transition metal-catalysed C–C bondforming reactions in flow, we envisaged the direct conversion of aryl iodides to the corresponding branched aldehydes via two sequential C–C bond-forming reactions by using three different reactive gases in a two-step telescoped process. To this end, we began by evaluating the hydroformylation of styrene itself (**41b**) by using the flow setup shown in Scheme 6.



Scheme 6. The gas-flow reactor configuration for optimisation of the rhodium-catalysed hydroformylation of styrene 41 b.

The flow reactor setup for this hydroformylation remained similar to that used for the ethylene Heck process. The only major alteration was substitution of the PFA reaction coil for a stainless steel coil. Our previous experience with flow hydrogenation^[7e] taught us that PFA is permeable to hydrogen gas, particularly at elevated temperature and will, therefore, be a poor choice of material for the hydroformylation reaction. Our current reactor design has remained stable and functional for over 400 experiments.

Styrene **41 b** (0.1 mmol) and the rhodium catalyst were dissolved in toluene (1 mL). This reaction plug was then injected through a sample loop and pumped at various rates through the gas–liquid reactor pressurised with syngas (CO/H₂ 1:1), followed by a heated stainless steel reaction coil. The exiting stream was then passed through a BPR, which was used to control the pressure of the system and ensure that the gases remained in solution. The initial catalyst screening data is shown (Table 9).

The results of the rhodium precatalyst and ligand^[27] screening experiments showed that, with PPh₃ as a ligand, Rh(CO)₂-(acac) was superior to Rh(OAc)₂ and Rh(PPh₃)₄. Furthermore, PPh₃ was the most effective ligand^[28] for our system compared to other phosphine and phosphite ligands [P(OPh)₃, P(o-Tol)₃, P(2-Fur)₃ (Tol = tolyl, Fur = furyl)], which all gave lower conversions. With an effective catalyst chosen, we began to screen for other parameters (Figure 3).

Table 9. Initial catalyst screening for the hydroformylation of styrene. ^[a]				
Entry	Metal	Ligand	Conv. [%]	Select. (b/l) ^[b]
1	Rh ₂ (OAc) ₄	P(2-Fur) ₃	9	95:5
2	Rh ₂ (OAc) ₄	PPh ₃	-	-
3	Rh ₂ (OAc) ₄	P(OPh) ₃	2	>99
4	Rh₂(OAc)₄	P(o-Tol) ₃	-	-
5	RhCl(PPh ₃) ₃	-	43	95:5
6	Rh(CO) ₂ (acac)	PPh ₃	63	94:6

[a] Styrene (0.1 mmol), rhodium source (3 mol%), ligand (18 mol%), toluene (1 mL), CO/H₂ (P=25 bar), AF 2400 (l=2 m), pump A (flow rate = 0.6 mL min⁻¹), 20 mL stainless steel coil, T=60 °C, t=33 min. [b] Selectivities of branched vs. linear (b/l) aldehyde products were determined by GC analysis.



Figure 3. Influence of a) temperature, b) flow rate, c) ligand loading and d) syngas pressure on selectivity and conversion in continuous flow styrene hydroformylations. General reaction conditions: 0.1 mmol styrene, Rh(CO)₂- (acac) (3 mol%), PhMe (1 mL), syngas (CO/H₂=1:1, P=20 bar, if not stated otherwise), 20 mL heating coil, T=60 °C (if not stated otherwise); a) AF 2400 (l=1 m), PPh₃ (30 mol%, catalyst prepared by using PhMe), flow rate=0.2 mL min⁻¹, t=100 min; b) AF 2400 (l=1 m), PPh₃ (6-30 mol%, catalyst prepared by using PhMe), flow rate=0.2 mL min⁻¹, t=100 min; d) AF 2400 (l=2 m), PPh₃ (18 mol%, catalyst prepared by using THF), flow rate=0.6 mL min⁻¹, t=33 min.

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The reaction temperature^[29] was first studied (Figure 3a). Not surprisingly, increasing the temperature to 80°C led to a significant increase in conversion. However, this was also accompanied by a loss of selectivity at temperatures above 60 °C. A good compromise temperature combining both high conversion and high selectivity was 65°C. Although the amount of ligand (relative to catalyst) did not seem to affect the conversion, it had a significant impact on regioselectivity with an improvement from 85:15 to 95:5 observed (Figure 3 c).^[30] Following this, we studied the effect that the pressure of syngas had on the reaction (Figure 3 d).^[31] As can be seen, not only did an increase in pressure result in an increased conversion, but this also produced an increase in linear/branched selectivity, with selectivities over 94% observed at 25 bar. Although a higher proportion of both gases would very likely enter the solvent stream at a higher pressure, it is unclear if changes in pressure would affect the ratio of H₂ to CO in solution. Under the conditions employed, the optimal flow rate was between 0.5 and 0.7 mLmin⁻¹. The fall in conversion at higher flow rates was not surprising because both the reaction time and the time given to the solvent to take up gas were reduced. The lower conversions at the lower end of the flow rate range were more unexpected (Figure 3b).

At this stage only a modest 57% conversion with 93:7 selectivity had been achieved after varying several parameters. To improve the situation we investigated the use of alternative solvents. Pleasingly, we found that running the reaction in methanol led to a significant increase in conversion to 79%. We were concerned about using this solvent in these reactions as it could react with the aldehyde products to form acetals, which would complicate matters greatly. Fortunately, however, we did not observe any products of acetal formation during these reactions. Additionally, the selectivity obtained with methanol was the same as that obtained with toluene. We found that the conversion could be increased further (to 93%) in this new solvent by increasing the reaction time (35 mL coil, 58 min) and by preparing the catalyst in a 1:1 mixture of methanol/toluene. The selectivity was also improved slightly to 94%.

Having identified conditions for high conversion and selectivity, we performed preparative reactions with a series of styrene derivatives by using the same apparatus as that shown in Scheme 6. The results of these experiments are shown in Table 10.

Not surprisingly, the conversions and selectivities observed in these reactions were significantly affected by the electronic properties of the aryl substituents.^[32] Those starting materials possessing electron-withdrawing substituents afforded products with higher conversions and selectivities than styrenes with electron-donating appendages. In addition to styrenes themselves, two hetero-styrenes were also subjected to these conditions. The 4-methyl-5-vinylthiazole derivative **46b** underwent highly selective hydroformylation in high conversion, whereas the 2-vinyl pyridine substrate **13b** also reacted in part through a hydrogenation side reaction pathway to afford 2ethylpyridine in significant quantities.



[a] Rhodium-catalysed hydroformylation of styrene derivatives. Reaction conditions: 1 mmol of substrate, Rh(CO)₂(acac) (3 mol%), PPh₃ (18 mol%), CO/H₂ (1:1, P=25 bar), substrate dissolved in 10 mL of PhMe/MeOH (1:1 mixture), flow solvent: MeOH (0.6 mLmin⁻¹), 65 °C. [b] Isolated yield of the branched regioisomer after flash chromatography. [c] Determined by GC analysis. [d] Complex reaction mixture: a significant amount of the 2-ethylpyridine was observed.

With the hydroformylation process established, the stage was set for combination with the ethylene Heck reaction in a telescoped two-step tandem flow process. Our initial results (Scheme 7) under a previous set of reaction conditions revealed that the process was possible.



Scheme 7. Flow setup for the Pd-catalysed vinylation of aryl iodides, followed by Rh-catalysed hydroformylation to afford branched aldehydes.

The palladium JohnPhos catalyst was used to catalyse the first ethylene Heck stage of the process. The Pd black precipitate formed during this transformation was removed by simple in-line filtration, thereby providing a reaction stream that was fed subsequently into a holding beaker and flushed with argon to remove excess dissolved ethylene, as done previously for the synthesis of unsymmetrical stilbenes. The resulting ethylene-free styrene solution was then injected in 1 mL portions through a 1 mL sample loop. This reaction stream containing 4-vinylanisole 5a was then combined with a second stream containing Rh(CO)₂(acac) (3 mol%) and Ph₃P (18 mol%) in methanol and toluene (1:1). The combined stream was then passed through a second gas-liquid reactor pressurised with syngas at 25 bar before entering a second heated stainless steel reaction coil. This preliminary experiment involving three different gases gave an encouraging 58% conversion and an excellent selectivity for the branched aldehyde of 94:6. The results suggested that a component of the ethylene Heck reaction stream (DMF, TBAI, Et₃N or Et₃NH⁺I⁻) may have hindered the subsequent hydroformylation process. Control experiments were performed on the hydroformylation step to investigate this possibility. Possible contaminants from the Heck reaction were introduced to the hydroformylation reaction of pure 4-methoxystyrene **5b**. The results are shown in Table 11.

Table 11. Screening of additives for disruption of the standard hydroformylation reaction. ^[a]				
Entry	Additive	Conv. ^[b] [%]	Select. ^[b] (b/l)	
1	-	81	9:1	
2	DMF 5% v/v	54	9:1	
3	TBAI 1 equiv.	28	9:1	
4	TBAI 0.1 equiv.	60	9:1	
5 ^[c]	[Pd] cat. 5 mol%	82	9:1	
[a] Standard rhodium-catalysed hydroformylation of styrene 5b as used in Table 10 with additives from the ethylene Heck product mixture. [b] Determined by ¹ H NMR analysis. [c] Catalyst composition: Pd(QAc)				

(5 mol%), tBu₃P·HBF₄ (10 mol%).

The presence of DMF or TBAI separately have a negative influence on the reaction, reducing the conversion to approximately that achieved in the initial telescoped reaction. However, no change in the selectivity was observed for any of the additives. The presence of $Pd(OAc)_2$ and $tBu_3P \cdot HBF_4$ together had no effect on the reaction. To streamline the two processes we decided to substitute the co-solvent for the ethylene Heck reaction for MeOH to match the solvent system used for the second hydroformylation process. To our delight, the use of an MeOH/PhMe (1:9) solvent system fully solubilised the TBAI and Cy₂NMeH⁺I⁻ salts and equivalent conversions were achieved for the ethylene Heck reaction. Furthermore, MeOH was found to negate the need to use TBAI, which was consequently removed from the reaction. Examples under these optimised conditions for the preparation of styrenes are given in Table 7. Despite the removal of two major inhibiting factors from the ethylene Heck reaction, hydroformylation of the optimised styrene output still gave a poor conversion. It was concluded that only remaining "foreign" reagent in the hydroformylation that was not screened against in Table 12, the Cy₂NMeH⁺I⁻ salt, might also have hindered the reaction process. The only method by which the salt and any excess base could be efficiently removed was to wash with aqueous acid solution. Achieving a truly continuous process from aryl iodide through to the branched aldehyde would therefore require an in-line liquid–liquid separation (LLS).^[20]

Recently in our laboratory, we developed a continuous flow liquid–liquid extractor (Scheme 8) and sought to incorporate this into the tandem process. The flow setup we used is shown in Scheme 9. The output stream containing styrene from the first reactor (1.0 mLmin^{-1}) is combined with a stream of aqueous HCl $(1 \text{ M}, 1.0 \text{ mLmin}^{-1})$ at a T piece followed by thorough mechanical mixing to form an emulsion. As the emulsion stream passes through the micro-tubing it rapidly separates into well-defined plugs of polar and non-polar solvent. The plug-flow stream is then injected into a separating column, which allows each plug to combine rapidly with its respective phase according to the specific gravity of the solvents

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[a] Isolated yield of the branched regioisomer after flash chromatography.
 [b] Conversion of iodide to styrene.
 [c] Conversion of styrene to branched and linear aldehydes.



Scheme 8. Continuous flow liquid–liquid extractor. The biphasic stream is injected into the glass Omnifit column below the phase interface.

(toluene as the top phase and methanol in water as the lower phase). The extraction of both base and methanol into the aqueous phase results in different flow rates of the organic



Scheme 9. Flow setup for the Pd-catalysed vinylation of aryl iodides, followed by Rh-catalysed hydroformylation to afford branched aldehydes, incorporating an in-line acid wash and extraction between reactions.

and aqueous output streams compared to the 1:1 ratio of the input streams. A webcam is used to constantly monitor the position of a coloured "float" (which sits at the interface) relative to the rest of the separating column and provide positional feedback through a control computer. If the position of the "float" varies from its defined optimum height, the flow rate of the pump removing aqueous waste is either increased or decreased to correct the level, so that the position of the interface is maintained constantly. In addition, the volume of organic phase in the separating column can be controlled by increasing the optimum height of the "float". Consequently, by decreasing this mixing volume any dispersion effects can be minimised. A fraction twice that of the original reaction plug size, to account for any dispersion and to effectively halve the reaction concentration, is collected in a holding beaker.

Excess ethylene was vented under argon before loading the fraction into an injection loop for the hydroformylation phase of the process. Notably, degasing of ethylene, which occurred in the LLS, caused no problems with the running of the device, as stated in our previous communication on the flow synthesis of hydroxyacids in which we were faced with the evolution of nitrogen gas.^[20b]

Conversions to the aldehydes achieved with the washed styrene fractions were equivalent to those achieved if using fresh styrene supplied commercially, supporting the hypothesis that the $Cy_2NMeH^+I^-$ salt (or its free base) was the inhibiting contaminant. However, the conditions reported in our earlier communication required the injection of 1 mL reaction plugs at spaced time intervals to achieve the best conversions and se-

lectivities, which was far from a continuous process. We had attributed this to the diffusion of gas from the surrounding solvent stream into the 1 mL reaction plug. As no optimisations were conducted after introducing methanol as co-solvent, which resulted in the dramatic increase in conversions, several parameters were reconsidered and it was discovered that decreasing the substrate concentration to $0.05 \,\mathrm{M}$ allowed for larger injection plugs and continuous flow. Furthermore, the change in concentration improved conversions whilst maintaining high selectivities. A range of branched aldehydes were synthesised directly from aryl iodides by using this tandem 2-step 3-gas process, as shown in Table 12.

lodides (entries 1–4, Table 12) showed improved conversions in the hydroformylation step with a lower substrate concentration. Particularly high selectivity (97:3) was observed for the 3iodobenzonitrile derivative **2a**. We had anticipated low overall isolated yields for two reasons: material could be lost either side of the collected fraction after LLS (unlikely, given the size of the fraction collected to halve the effective concentration) or the extraction of methanol into the aqueous phase could have improved the solubility of styrene in the polar phase resulting in the loss of some material by extraction. Despite these concerns, the isolated yields for the telescoped process were only marginally below those obtained from the single step process.

Conclusions

We have developed a gas-liquid flow system for the palladium-catalysed ethylene Heck process that, by delivering gas to flow streams as homogeneous solutions, facilitated the rapid screening and optimisation of conditions in a safe and controllable manner. The optimised conditions were used to transform a variety of aryl and heteroaryl iodides into synthetically valuable styrene derivatives in high conversions and yields. Reactions were performed on scales from 0.3 to 120.0 mmol by using the same system, highlighting the ease of scale-out for these continuous flow devices. The permeation and take-up of ethylene by the solvent was quantitatively measured by using an in-line ReactIR flow cell calibrated by using a gas burette. It was found that the gas concentration was linearly proportional to pressure and exhibited saturation behaviour with respect to time, as might be expected. By using controlled depressurisation and argon flushing, the excess ethylene gas could be removed to facilitate a second Heck cross-coupling with no additional catalyst to afford unsymmetrical stilbenes in a tandem two-step telescoped flow process. By using the same gasliquid flow devices, an efficient and highly selective continuous flow hydroformylation process was developed that facilitated the rapid and scalable synthesis of synthetically useful α branched aldehydes from styrene precursors. As only small volumes of pressurised syngas (CO/H₂ 1:1) were present in the reactor at any one time, the safety profile of the process was enhanced greatly, highlighting one of the key advantages of flow chemistry compared with batch mode. Initial attempts to telescope the two transformations into a 3-gas 2-step tandem flow process identified that a component of the first reaction mixture was inhibiting the second reaction. This incompatibility was resolved by the incorporation of our recently developed in-line liquid–liquid extraction system to remove the offending component between the two steps. The overall yields of branched aldehydes from the two-step telescoped process are comparable to those achieved in the hydroformylation of pure styrene starting materials. This is only possible with the high conversions achieved in the ethylene Heck process and efficient washing and separation operations in-line prior to the hydroformylation step.

The rapid optimisation of these processes and their incorporation into telescoped tandem flow processes highlights the importance (especially in the context of the research laboratory) of the flexibility and modularity that these newly developed flow chemistry technologies provide.

Experimental Section

Synthesis of unsymmetrical stilbenes from aryl iodides

General procedure: The first aryl iodide (0.6 mmol), Cy₂NMe (2.2 equiv.), Pd(OAc)₂ (1 mol%) and tBu₃P·HBF₄ (2 mol%) were dissolved in MeOH/PhMe (1:9, 3 mL, 0.2 M). The 3 mL reaction mixture was injected into a Uniqsis Flowsyn reactor through a 10 mL PEEK injection loop A. The reaction plug was pumped at 1 mLmin⁻¹ (stock solvent MeOH/PhMe 1:9) by using a tube-in-tube gas reactor (l = 1.5 m, AF 2400) pressurised with 10 bar ethylene followed by a 20 mL PTFE reaction coil at 130 °C (residence time = 20 min). The exiting reaction stream passed through a BPR (P = 20 bar) and a 6 mL fraction (containing the reaction plug and any dispersion) was collected and flushed with argon. After degassing with argon for 5 min, the 6 mL reaction mixture was injected a second time through injection loop A at a flow rate of 0.2 mLmin⁻¹ and combined with a 6 mL solution of the second aryl iodide from injection loop B at a flow rate of 0.2 mLmin⁻¹ at a T piece mixer. The reaction stream entered a 20 mL reaction coil at 130 $^\circ\text{C}$ (residence time = 50 min) and exited through a BPR (P = 20 bar). The crude reaction solution was worked up with aqueous HCl and brine in batch mode, followed by column chromatography.

Synthesis of branched aldehydes from aryl iodides

General procedure: The procedure for the formation of styrene from aryl iodides was identical to that used for the synthesis of unsymmetrical stilbenes, except that 1.2 equiv. instead of 2.2 equiv. of base was used. The exiting reaction stream from the reaction 1 (1 mLmin⁻¹) was combined with an aqueous HCl (1 m) stream (1 mLmin⁻¹) at a T piece. The combined biphasic stream was then passed through an in-line mechanical mixer followed by an in-line liquid-liquid separator (full details in the Supporting Information). (At this stage the styrenes could be purified by small-scale distillation.) A 6 mL organic fraction was collected from the LLS and flushed with argon in a holding flask for 5 min. The reaction mixture was then injected through injection loop A at a flow rate of $0.3 \; mLmin^{-1}$ (stock solvent MeOH/PhMe 1:1) and combined with a 6 mL solution of Ru(CO)₂(acac) (3 mol%) and PPh₃ (18 mol%) dissolved in MeOH/PhMe (1:1), which was injected through injection loop B at a flow rate of 0.3 mLmin⁻¹ at a T piece mixer. The reaction stream then entered a tube-in-tube gas reactor (l = 1.5 m, AF 2400) pressurised with syngas (CO/H₂ 1:1, P = 25 bar) followed by a 30 mL stainless steel reaction coil at $70\,^{\circ}$ C (residence time = 50 min) and exited through a BPR (P=28 bar). The crude reaction mixture was then purified by column chromatography.

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