Syngas-Mediated C–C Bond Formation in Flow: Selective Rhodium-Catalysed Hydroformylation of Styrenes

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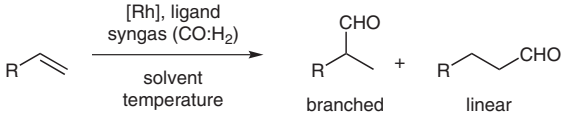
Abstract: We report a continuous flow, rhodium-catalysed hydroformylation of various styrenes using a tube-in-tube gas–liquid reactor. The flow process afforded selectively branched aryl aldehydes in good yields.

Key words: hydroformylation, rhodium, catalysis, membrane, flow

Hydroformylation is a powerful carbon–carbon bond forming reaction,[1] whereby one molecule of CO and H_2 are added across an olefinic bond to afford synthetically versatile aldehyde products (Scheme 1).



Scheme 1 General scheme for the rhodium-catalysed hydroformylation of alkenes providing branched and linear aldehydes

The reaction is highly atom-efficient. However, while no atoms are lost as waste in the reaction itself, hydroformylation processes typically require an excess of both gases and high pressures to achieve efficient catalyst turnovers. Fortunately, CO and H_2 are plentiful and inexpensive reagents, which have enabled hydroformylation to become the largest-scale application of homogeneous catalysis today.[2]

Whilst many industrial applications of hydroformylation afford linear aldehydes,[3] the branched isomer,[4] which leads to greater molecular complexity, is less straightforward to construct and often requires inefficient syntheses. Varying the electronic nature of substituents attached to the alkene can strongly influence the selectivity of the reaction. Aromatic alkenes and vinyl ethers generally provide branched aldehydes[5] with high regioselectivities, while aliphatic alkenes generally yield linear products.[6] Despite the appeal of this efficient C–C bond-forming reaction, it is not commonly employed in research laboratories[7] owing to the flammable and toxic properties of the gases involved. In addition, the impractical nature of using high pressure batch equipment necessitates the development of alternative approaches.

Flow chemistry has emerged over recent years as an enabling technique that often enhances the safety profile of synthetic processes, particularly those that involve hazardous conditions (e.g., high temperature or pressures) and intermediates.[8] We have previously reported on the advantages of using gas-permeable membrane[9] based reactors for gas–liquid reactions[10] in continuous-flow mode, compared to other flow chemistry methods.[11] The small internal volume of the reactor greatly enhances the safety profile of the reaction and makes hydroformylation reactions easy and safe to carry out in research laboratories.

We report here the hydroformylation of functionalised styrenes in flow using a tube-in-tube gas–liquid flow reactor, which efficiently delivers gas to a liquid stream. The study was initiated by evaluating the hydroformylation of styrene (**1a**) using the flow setup shown in Figure 1.

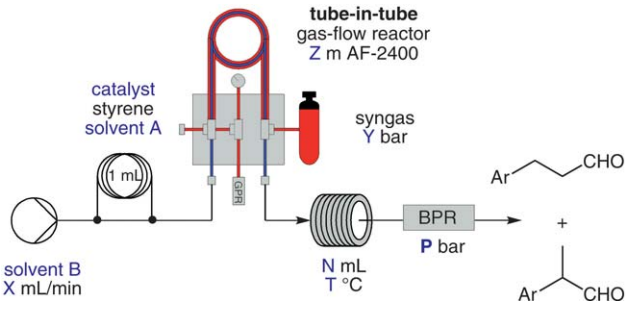


Figure 1 Gas-flow reactor configuration for optimisation of the rhodium-catalysed hydroformylation of styrene (**1a**)

A commercially available flow system was used to pump the reaction mixture to the gas–liquid reactor from a 1 mL PTFE sample loop (although any suitable flow chemistry platform can be used). Styrene (**1a**; 0.1 mmol) and the rhodium catalyst were dissolved in solvent (1 mL). The rhodium pre-catalyst and ligand were premixed in anhydrous solvent before adding olefin to the mixture. This reagent stream was then pumped at various rates through the gas–liquid reactor pressurised with syngas (CO/H_2 = 1:1), followed by a heated stainless steel reaction coil. The exiting stream was then passed through a back-pressure regulator (BPR), which is essential to prevent outgassing

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from the solution in the reactor and to maintain a homogeneous solution, thus avoiding segmented flow. The initial optimisation reactions are summarised in Figure 2. In this screening process we focused on reaction parameters including rhodium catalyst/loading, gas pressure, reaction temperature, flow rate and solvent. The results of the rhodium pre-catalyst and ligand[12] screening showed that [$Rh(CO)_2(acac)$] gave the best conversions compared to $Rh(OAc)_2$ and $Rh(PPh_3)_4$ when Ph_3P was used as a ligand. Furthermore, Ph_3P proved to be the most effective ligand[13] for our system when compared to other phosphorous ligands [$P(OPh)_3$, P(*o*-Tol)$_3$, P(2-fur)$_3$], which gave low conversions.

Having established the optimal catalyst and its loading (3 mol%) for flow hydroformylation, the reaction temperature[14] was then investigated (Figure 2, **A**). Higher conversions were observed with increasing temperature up to 80 °C. However, the selectivity was adversely affected beyond 60 °C. The optimal combination of high conversion and high selectivity was achieved at 65 °C. In a screen to determine the optimal catalyst to ligand ratio, it was found that increasing the amount of Ph_3P ligand led to a regioselectivity improvement from 85:15 to 92:8 of branched to linear aldehydes (Figure 2, **C**).[15] Thereafter, the effect of varying the pressure of syngas in the tube-in-tube reactor was investigated (Figure 2, **D**).[16] Modest conversions were achieved at lower pressures, while at 25 bar of syngas the conversion of styrene to aldehyde improved significantly (with increased selectivity). Varying the flow rate between 0.1 mL/min and 1.0 mL/min (Figure 2, **B**) revealed that the conversion was optimal between 0.5 and 0.7 mL/min. At higher flow rates the conversion decreased, possibly due to a combination of shorter reaction time and insufficient dissolution of gas into the liquid stream. Reactions performed at lower flow rates gave unexpectedly low conversion into the desired aldehydes. After this initial screening, the best conversion obtained was 57% (Figure 2, conditions **D**, 25 bar of syngas) with 93:7 regioselectivity.

The influence of solvent was then examined. Changing the reaction solvent from toluene to methanol resulted in a dramatic increase in conversion to 79% without loss of selectivity. Although methanol is not traditionally used in hydroformylations due to its tendency to form acetal products through further reaction with the aldehydes,[17] no such by-products were observed and only the desired aldehydes were obtained. Further adjustments to the reaction time (35 mL coil, 58 min) and the solvent used for catalyst preparation (MeOH–toluene, 1:1) gave excellent conversion (93%) of styrene (**1a**) into the desired aldehyde with high selectivity (B/L = 94:6). With optimised reaction conditions in hand, the scope of the process was investigated. Yields and selectivities for the hydroformylation of a variety of styrene derivatives are shown in Table 1. The flow setup used for the synthesis of the examples was the same as that used in Figure 1 for the optimisation reactions.

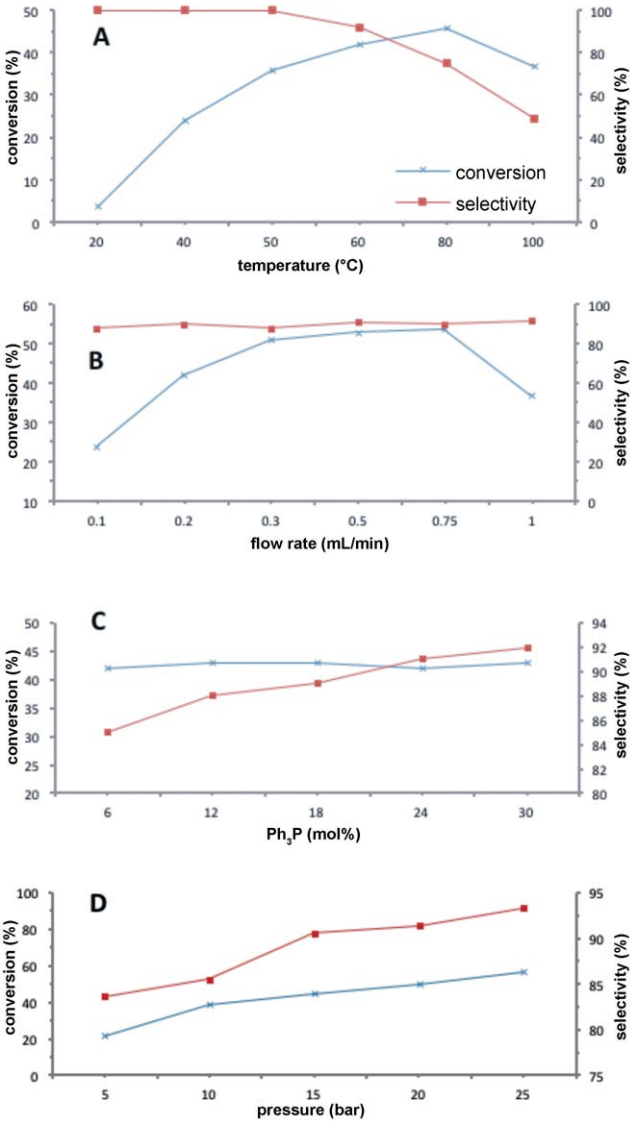


Figure 2 Temperature (**A**), flow rate (**B**), ligand loading (**C**) and pressure of syngas (**D**) influence on selectivity and conversion in continuous flow styrene hydroformylation. *General reaction conditions*: styrene (0.1 mmol), [$Rh(CO)_2(acac)$] (3 mol%), 1 mL loop, 20 bar (CO/H_2 = 1:1) (if not stated otherwise), 20 mL heating coil, 60 °C (if not stated otherwise), toluene; **A**: AF-2400 1 m, Ph_3P (30 mol%) (catalyst prepared using toluene), flow rate: 0.2 mL/min, reaction time: 100 min; **B**: AF-2400 1 m, Ph_3P (24 mol%) (catalyst prepared using toluene); **C**: AF-2400 1 m, Ph_3P (6–30 mol%) (catalyst prepared using toluene), flow rate: 0.2 mL/min, reaction time: 100 min.; **D**: AF-2400 2 m, Ph_3P (18 mol%) (catalyst prepared using THF), flow rate: 0.6 mL/min, reaction time: 33 min.

The electronic properties of the aryl substituents on the styrene compounds had an effect on the reaction conversions and selectivities.[18] Styrene substrates with electron-withdrawing groups gave the desired aldehydes in higher conversions and better regioselectivities than those bearing electron-donating groups. Furthermore, two different heteroaromatic styrenes were tested. Hydroformylation of 2-vinyl pyridine (**11a**) gave predominantly the branched aldehyde, however, a significant amount of the hydrogenated by-product 2-ethylpyridine was observed (Table 1, entry 11). Hydroformylation of 4-methyl-5-vinylthiazole

(**12a**) gave the branched aldehyde with high conversion and regioselectivity (Table 1, entry 12). It is noteworthy that all the reactions were highly reproducible in terms of conversion as well as regioselectivity.

Concurrent investigations in our group have led to the development of an efficient method for the preparation of functionalised styrenes via a palladium-catalysed cross-coupling of aryl iodides with ethylene gas.[19] To demonstrate the potential of transition-metal-catalysed C–C bond-forming reactions in flow, we envisaged the direct conversion of aryl iodides into the corresponding branched aldehydes via two sequential C–C bond-forming reactions using reactive gases (Figure 3).

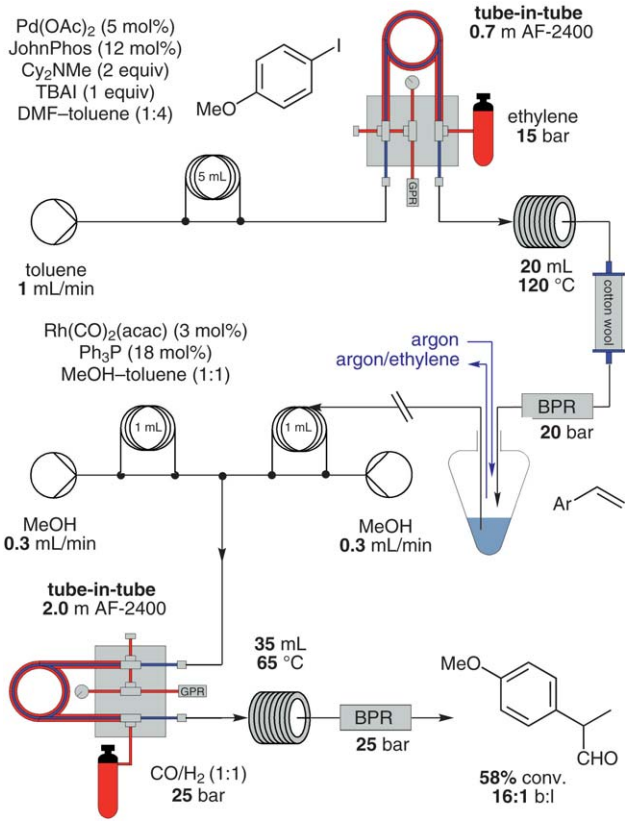
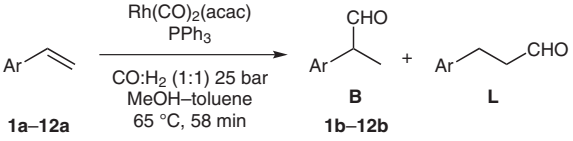
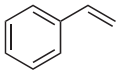
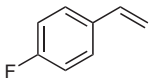
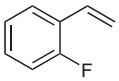
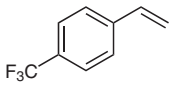
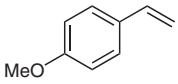
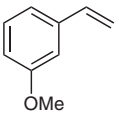
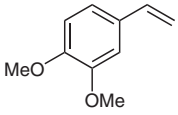
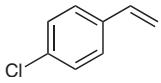
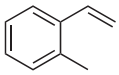
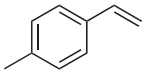
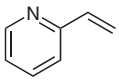
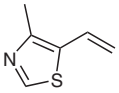


Figure 3 Flow setup for the Pd-catalysed vinylation of aryl iodides followed by Rh-catalysed hydroformylation to afford linear and branched aldehydes

Although alternative complexes that maintain complete homogeneity throughout the reaction can be used to catalyse the Heck reaction, the palladium JohnPhos complex forms significant amounts of palladium black as it catalyses the vinylation of 4-iodoanisole to 4-vinylanisole; however, this can be easily removed through simple in-line filtration, thereby providing a reaction stream that can be fed directly into the continuous flow hydroformylation after the removal of ethylene gas.[20] Subsequently, the reaction stream containing 4-vinylanisole (**5a**) was added to a third stream containing [$Rh(CO)_2$(acac)] (3 mol%) and Ph_3P (18 mol%) in MeOH and toluene (1:1). The stream was then passed through a second gas–liquid reactor pressurised with syngas (CO/H_2 = 1:1) at 25 bar before entering a second heated stainless steel reaction coil. This preliminary experiment, involving three different gases,

Table 1 Rhodium-Catalysed Hydroformylation of Styrene Derivatives **1a–12a**[a]



Entry	Substrate	Conv. (%)[b,d]	B/L[b,d]	Yield (%)[c,d]
1		90	13:1	71
2		89	12:1	82
3		95	16:1	86
4		97	31:1	94
5		81	9:1	75
6		93	13:1	85
7		92	10:1	80
8		96	18:1	70
9		90	6:1	69
10		86	11:1	69
11		–	–	–[e]
12		95	23:1	81

[a] Reaction conditions: substrate (1 mmol), [$Rh(CO)_2$(acac)] (3 mol%), Ph_3P (18 mol%), 25 bar of CO/H_2 (1:1), substrate dissolved in 10 mL of toluene–MeOH (1:1 mixture), flow solvent: MeOH (0.6 mL/min).
[b] Determined by GC analysis.
[c] Isolated yield of the branched regioisomer after purification by flash chromatography on silica gel.
[d] Values correspond to results obtained after two runs with each substrate.
[e] Complex reaction mixture: a significant amount of the 2-ethylpyridine was observed.

gave a reasonable 58% conversion and an excellent selectivity for the branched aldehyde of 16:1.

In conclusion, we have developed an efficient, high-yielding and highly regioselective continuous flow hydroformylation process using a tube-in-tube gas–liquid reactor. This reactor, which is based on the semi-permeable polymer Teflon AF-2400, reliably and controllably generates homogeneous solutions of gas in liquid, thereby facilitating rapid optimisation. To further demonstrate the usefulness of these reactors for carbon–carbon bond-forming reactions involving gases, an ethylene Heck reaction has been linked with the hydroformylation described in this paper to form two carbon–carbon bonds in a multi-step flow process.

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(20) The styrene product fraction (~5 mL) was collected in a sample vial under a steady stream of argon to remove ethylene gas from the solution. After fraction collection (~5 min), argon was bubbled through the reaction solution for a further 5 min. The solution was then loaded into the 1 mL sample loop in preparation for the hydroformylation.