The Continuous-Flow Synthesis of Styrenes Using Ethylene in a Palladium-Catalysed Heck Cross-Coupling Reaction

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Abstract: We report a palladium-catalysed ethylene Heck reaction for the vinylation of aryl iodides using a tube-in-tube gas–liquid reactor. The flow process afforded various styrenes in short reaction times, employing moderate ethylene pressure.

Key words: vinylation, membrane, flow, ethylene, styrene

In recent years the furtherance of green chemistry[1] initiatives has encouraged the development of more economically beneficial and environmentally benign processes. An important consideration therefore, becomes the atom and step economy[2] of new synthetic processes.

As it becomes more apparent that many traditional batch methods are not sustainable for future applications, new technologies and tools for synthesis have evolved that display demonstrable advantages. In particular, flow chemistry[3] has received a great deal of attention from the scientific community over the past decade. Continuous-flow techniques can often provide better mixing and heat transfer, precise control over concentrated or hazardous reaction streams, reduced solvent waste and synthetic shortcuts. Moreover, the rapid process optimisation of synthetic steps on a small scale, combined with the telescoping of steps together in a continuous fashion, enables far less wasteful multistep sequences to be performed, leading directly to drug molecules[4] or even natural products.[5]

We envisage combining continuous-flow technologies with the use of reactive gases as a means to incorporate small gaseous building blocks into molecules, thereby simplifying work-up procedures and affording cleaner overall syntheses.

We have previously reported upon the application of a gas permeable membrane (Teflon AF-2400)[6] reactor, such as the device in Figure 1, for facilitating the transfer of ozone,[7a] oxygen,[7b] carbon dioxide,[7c] carbon monoxide[7d] or hydrogen[7e] into a reagent stream in a controlled manner. Consequently, the safety concerns associated with using reactive gases with conventional high-pressure batch equipment (such as uncontrolled depressurisation, flammability and toxicity) are mitigated due to the small internal volume of the device and its isolation from the main cylinder.

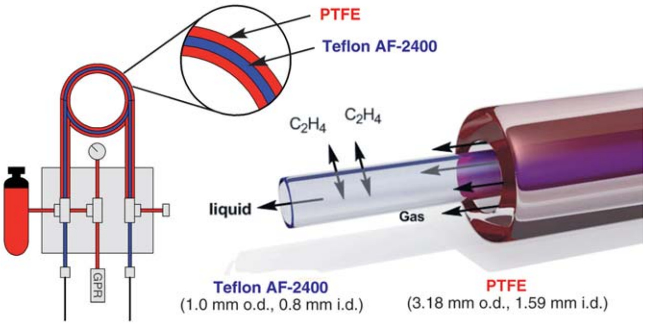
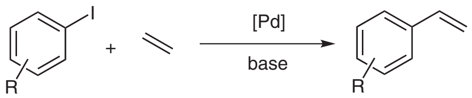


Figure 1 Tube-in-tube semi-permeable membrane gas–liquid reactor

We report here a Mizoroki–Heck-type cross-coupling of aryl iodides with ethylene gas to furnish functionalised styrenes in flow (Scheme 1). Styrenes have been recognised as useful intermediates that can undergo further transformations such as epoxidation,[8] cyclopropanation,[9] Heck coupling[10] and hydroformylation.[11] However, despite the many potential applications of styrenes in synthesis and given the plethora of literature reports on palladium-catalysed C–C bond-forming reactions since the initial work of Mizoroki[12] and Heck,[13] the development of a practical ethylene Heck process[14] has been hindered due to the general reluctance to use reactive gases in research laboratories. Established high-yielding syntheses of styrenes, starting from aryl halides, currently involve the palladium-catalysed insertion of vinyl metal species such as potassium vinyltrifluoroborate[15] or vinyltributyltin.[16] However, these are associated with toxicity, expense, difficult work-up procedures and significant amounts of waste.



Scheme 1 General Heck cross-coupling reaction of aryl iodides with ethylene gas to afford styrenes

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The study reported here was initiated by evaluating the vinylation of 3-iodoanisole (**1a**) using the flow chemistry arrangement shown in Figure 2. A commercially available flow system was used to pump the reagents to the gas–liquid reactor from a 5 mL PEEK sample loop. Iodide **1a** (0.5 mmol), triethylamine (2 equiv), additive (1 equiv) and the catalyst (5 mol%) were dissolved in solvent (5 mL). This reagent stream was then pumped at a rate of 1 mL/min through the gas–liquid reactor, pressurised with ethylene at 15 bar, followed by a 20 mL heated PFA reaction coil at 120 °C, after which the exiting stream passed through a plug of cotton wool, to remove Pd black, then through a 20 bar back-pressure regulator (BPR; Figure 2).

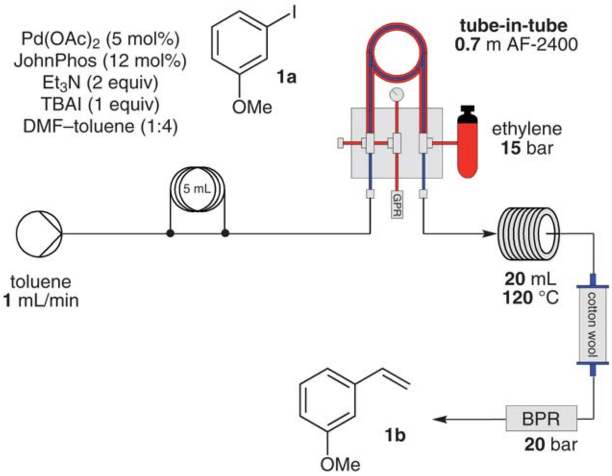


Figure 2 Flow set-up for the ethylene Heck optimisation using 3-iodoanisole

Our initial optimisations focused on preventing Pd black formation to achieve completely homogeneous reaction solutions. Previous work in our group on carbonylation reactions[7e] in flow had shown that the palladium XantPhos complex resisted rapid formation of Pd black. Although the XantPhos ligand is not popularly used for Heck-type reactions, it did allow for a rapid initial optimisation without the added complication of blockages and filter-changes in a sealed, super-heated system. Conditions were varied according to reaction time, reaction concentration, ethylene pressure and temperature. The best conditions from this initial optimisation were used to screen alternative ligands more commonly employed in Heck-type reactions (Table 1).

The monodentate ligands t-Bu$_3$P and Ph$_3$P also prevented any formation of Pd black (Table 1, entries 5 and 6). However, low conversion was observed for both. The Buchwald-type ligands[17] XPhos and SPhos also gave low conversions, with the exception of JohnPhos, which gave a 46% conversion, although accompanied by the formation of minor amounts of Pd black. Thereafter, the use of tetraalkylammonium salts[18] was investigated, for which it was necessary to use a mixed solvent system with *N*,*N*-dimethylformamide to completely dissolve the additives. It was found that the addition of *N*,*N*-dimethylformamide alone improved the conversion to 54%, and the addition of tetrabutylammonium iodide (TBAI, 1 equiv; Table 1, entry 9) gave 96% conversion. Minor amounts of Pd black formation presented no problems.

Table 1 Optimisation of the Reaction[a]

Entry	Ligand (mol%)		Additive (equiv)	Conv. (%)[b]
1	XantPhos	(6)	–	36
2	JohnPhos	(12)	–	46
3	SPhos	(12)	–	5
4	XPhos	(12)	–	10
5	t-Bu$_3$P	(15)	–	25
6[c]	Ph$_3$P	(15)	–	–
7[d]	JohnPhos	(12)	–	54
8[d]	JohnPhos	(12)	n-Bu$_4$NOAc (1)	60
9[d]	JohnPhos	(12)	n-Bu$_4$NI (1)	96

[a] Et$_3$N (2 equiv), Pd(OAc)$_2$ (5 mol%), dioxane (0.1 M), 120 °C, 50 min, ethylene (15 bar)

[b] Conversions determined by ^{1}H NMR analysis.

[c] No reaction was observed.

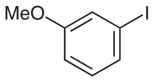
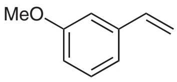
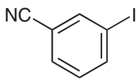
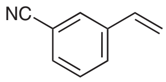
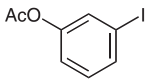
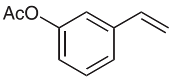
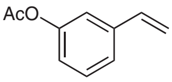
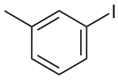
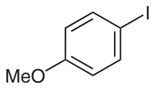
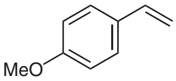
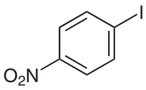
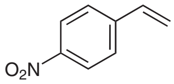
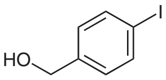
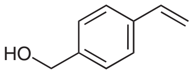
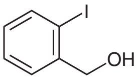
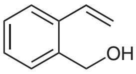
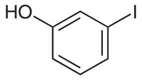
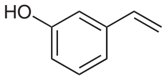
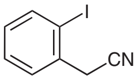
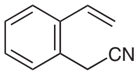
[d] DMF in dioxane (1:4) was used as solvent.

A brief investigation into alternative solvent systems revealed that toluene gave equivalent or better conversions than dioxane. Therefore, the solvent system was changed to *N*,*N*-dimethylformamide in toluene (1:4).

A variety of substituted aryl iodides were examined in the coupling reaction with ethylene, as shown in Table 2. Substrates with both electron-withdrawing and electron-donating substituents furnished the corresponding styrene products in good isolated yields. Hydroxy groups, including benzyl alcohols, were also compatible with the reaction (Table 2, entries 7–9). Substrate **6a**, with a strongly electron-withdrawing *para*-nitro group, gave the styrene product in only 60% conversion.

The reactions shown in Table 2 had residence times of 20 min. We had found earlier that a 50 min residence time (using a lower flow rate), counter-intuitively led to decreased conversions. To investigate the dissolution of ethylene in the solvent stream as a function of pressure and flow rate, an in-line ReactIR® flow cell was used.[19] The asymmetrical CH$_2$ bend observed in the IR spectra at 952 cm^{-1} was used to measure the ethylene concentrations [calibrating the IR data with gas burette measurements showed that a difference in absorption of 0.01 A.U. corresponds to a concentration difference of 1.48 mL (0.066 M) of ethylene gas per 1 mL of toluene].

Table 2 Scope of the Reaction[a]

Entry	Substrate	Product	Yield[b] (conv.)
1	 **1a**	 **1b**	80% (94%)
2	 **2a**	 **2b**	83% (99%)
3	 **3a**	 **3b**	71% (82%)
4	 **4a**	 **4b**	73% (87%)
5	 **5a**	 **5b**	85% (98%)
6	 **6a**	 **6b**	43% (60%)
7	 **7a**	 **7b**	78% (88%)
8	 **8a**	 **8b**	76% (94%)
9	 **9a**	 **9b**	75% (92%)
10	 **10a**	 **10b**	81% (95%)

[a] Reaction conditions: Aryl iodide (0.5 mmol), Et_3N (2 equiv), $Pd(OAc)_2$ (5 mol%), JohnPhos (12 mol%), TBAI (1 equiv), DMF in toluene (1:4), 120 °C, 20 min, 1 mL/min, ethylene (15 bar), AF-2400 (0.7 m).

[b] Isolated yield after distillation.

As can be seen from the results shown in Figure 3, a higher ethylene concentration is obtained at lower flow rates, and the ethylene concentration at a fixed flow rate increases linearly with ethylene pressure, as expected. The reason lower conversions were observed at longer retention times is not yet clear, investigations are continuing.

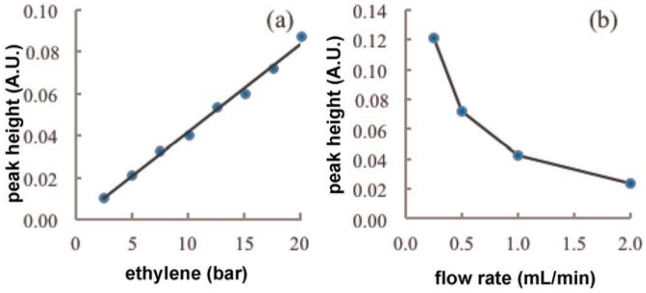


Figure 3 (a) Intensity of ethylene stretching frequency at 952 cm^{-1} against pressure at constant flow rate (1.0 mL/min). (b) Absorbance of ethylene against flow rate at constant pressure (10 bar).

To further demonstrate the potential of homogeneous transition-metal-catalysed C–C bond-forming reactions performed in flow, we envisaged telescoping the ethylene Heck into a second Heck reaction (Figure 4), whereby the easy removal of ethylene gas followed by the addition of a second aryl iodide would afford unsymmetrical stilbenes using catalyst turned over from the initial step. Consequently, it was necessary to prevent the formation of Pd black. The ligands *t*-Bu_3P and Ph_3P were reinvestigated and it was found that *t*-Bu_3P gave equivalent or better conversions than JohnPhos in the presence of TBAI and Cy_2NMe without the formation of Pd black. This provided a robust catalyst system that could be turned over and used to catalyse the second Heck reaction without loss of activity due to palladium black formation.

The reaction stream containing the styrene product of Ar^1I was collected in a vented flask and degassed by flushing with excess argon. The solution was then combined with a second stream containing Ar^2I (1 equiv) at a T-piece before entering a second heated reaction coil to effect a second Heck cross-coupling reaction.

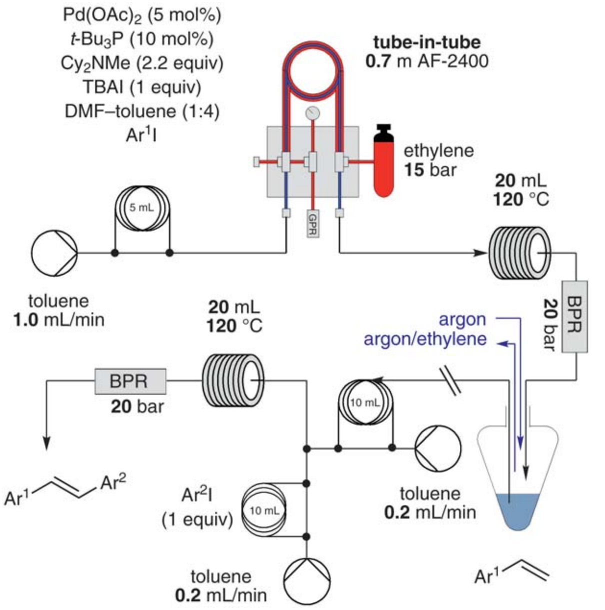
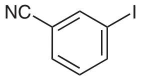
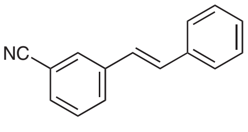
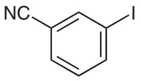
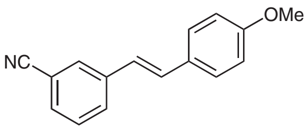
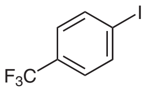
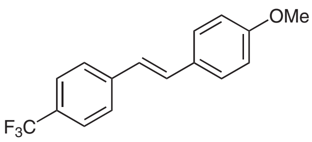
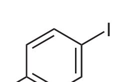
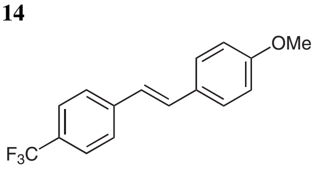


Figure 4 Flow set-up for the vinylation Ar^1I followed by a second Heck reaction with Ar^2I to afford unsymmetrical stilbenes

Table 3 Unsymmetrical Stilbenes

Entry	Starting iodide	Product	Yield[a] (Conv.)
1	 **2a**	 **12**	72% (92%)
2	 **2a**	 **13**	73% (81%)
3	 **11**	 **14**	68% (92%)
4	 **5a**	 **14**	(25%)[b]

[a] Isolated yield after distillation.

[b] 99% conversion into 4-vinyl styrene; however, poor olefin reactivity gave low stilbene conversion.

Specific aryl iodides were selected for the first coupling reaction with ethylene to ensure that there was minimal unreacted starting material remaining that could lead to homo-coupled by-products. The synthesis of the 4-trifluoromethyl styrene intermediate also illustrates that volatile styrenes that would otherwise be difficult to isolate can easily be telescoped into a second reaction. While, in principle, any combination of aryl iodides can be used, the reactivity of the styrene formed needs to be considered. Stilbene **14** can be synthesised by first forming 4-trifluoromethyl styrene or 4-vinylanisole, however, the latter (Table 3, entry 4) is less favoured for the second coupling reaction.

In conclusion, a fast, safe and practical preparation of functionalised styrenes via a palladium-catalysed cross-coupling of aryl iodides and ethylene gas has been developed. The safety concerns regarding the use of pressurised ethylene gas are mitigated by employing the continuous flow tube-in-tube gas–liquid reactor to administer the gas in a controlled manner. The amount of ethylene gas in the reagent stream was quantified using in-line IR analysis, allowing precise control of ethylene stoichiometry. Moreover, the ethylene Heck process can be telescoped with a second Heck reaction, with effective turnover of the initial catalyst system to afford unsymmetrical stilbene products.

Further work is underway to optimise the coupling reaction with ethylene for alternative substrates, in addition to optimising the second telescoped reaction. Furthermore, it has been possible to link the ethylene Heck reaction with a hydroformylation in flow to prepare branched aldehydes, thereby demonstrating the sequential use of reactive gases (see the succeeding paper).[20]

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