Synthesis of *Pterostilbene* through supported-catalyst promoted Mizoroki-Heck reaction, and it's transposition in continuous flow reactor.

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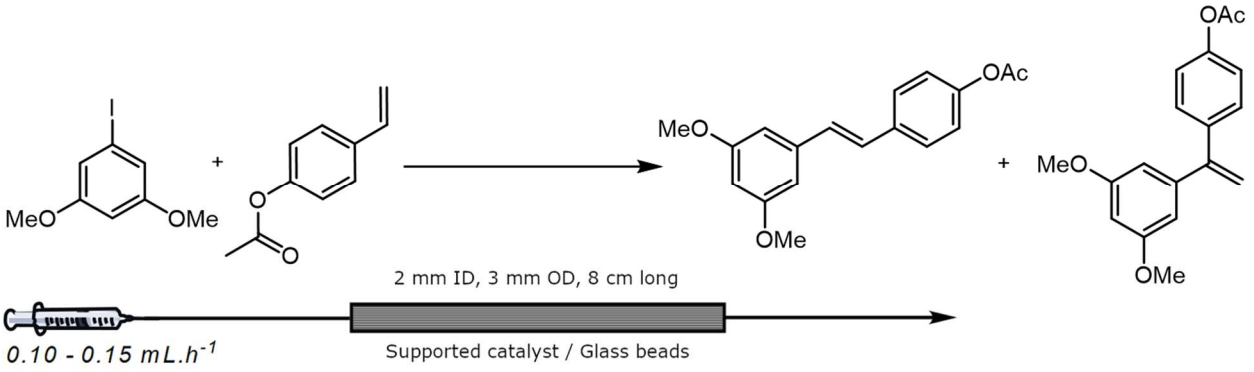
ABSTRACT

Pterostilbene, an important polyphenolic compound with interesting biological activities, has been efficiently synthesized through a Mizoroki-Heck reaction catalyzed by supported Palladium catalyst. The synthesis has been transposed in a continuous flow reactor, following two different retrosynthetic approaches.

TOC/Abstract Graphic

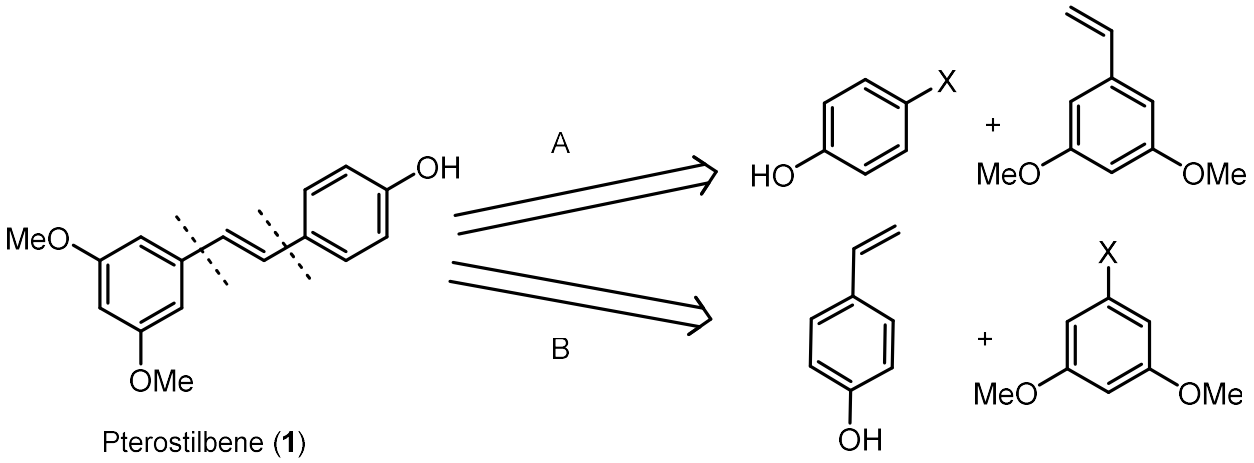


INTRODUCTION

Pterostilbene, 3,5-dimethoxy-4'hydroxystilbene (**1**), is a non-flavonoid polyphenolic compound of natural derivation, a methoxylated analog of the most iconic Resveratrol. It has been found as a secondary metabolite in several fruits, leaves and plants, including *Vitis Vinifera*, in response to environmental stress and fungal infections. Like Resveratrol and other molecules of the stilbene family, **1** shows several interesting pharmacological properties,[1] including chemopreventive,[2] anti-inflammatory,[3] antifungal,[4] and anticancer[5] effects. For more complete descriptions on the metabolic pathways[6] involving Pterostilbene and to it's several bio-medical applications,[7] we refer to more specific reviews and included references. However, it's important to highlight that very recently, **1** has been extensively clinically tested for antioxidant [8] and antiobesity activity,[9] cancer prevention[10] and therapy,[11] showing often a major bio-availability respect to Resveratrol.[12] The presence of the two methoxyl groups in **1** indeed enhance the lipophilicity of the molecule, resulting in a higher absorption rate in cells. Given its promising properties, no wonder that, many

attempts were made to achieve a green and sustainable synthesis of Pterostilbene, and of the other stilbenoids. Three main strategies have been proposed in the past years. The first one is based on a Perkin condensation followed by a decarboxylation step. In 2009 Zou *et al*. synthesised some stilbenoid derivatives in good yields, using a large excess of copper and quinoline.[13] Afterwards the same authors were able to improve the synthesis using a microwave reactor, polyethylene glycol as a solvent, phenantroline and catalytic copper.[14] The second strategy is based on olefination reactions. Westwell *et al*. for example, used the Horner-Wadsworth-Emmons reaction, to synthesise several polyphenolic compounds, from protected hydroxy-aldehydes and aryl diethoxy phosphonates.[15] A similar approach was used by McNulty and McLeod, improving the general sustainability of the process, utilizing a partially stabilized ylide.[16] Notably in literature is present also an attempt to synthesise **1** through a Julia olefination, which leads to a mixture of hydroxyl protected and deprotected compounds.[17] Probably, the most appealing strategy, is the cross-coupling through a Mizoroki-Heck reaction, as the supported catalyst approach can be envisioned, and the building blocks are low-cost commercially available materials. This method has been, indeed, already widely employed to synthesise Resveratrol, with different procedures.[18,19] Alkenyl Heck reaction to obtain **1** can proceed through two different retrosynthetic pathways, as shown in Scheme 1.

Scheme1. Retrosynthetic pathways of **1** through Mizoroki-Heck cross-coupling reactions



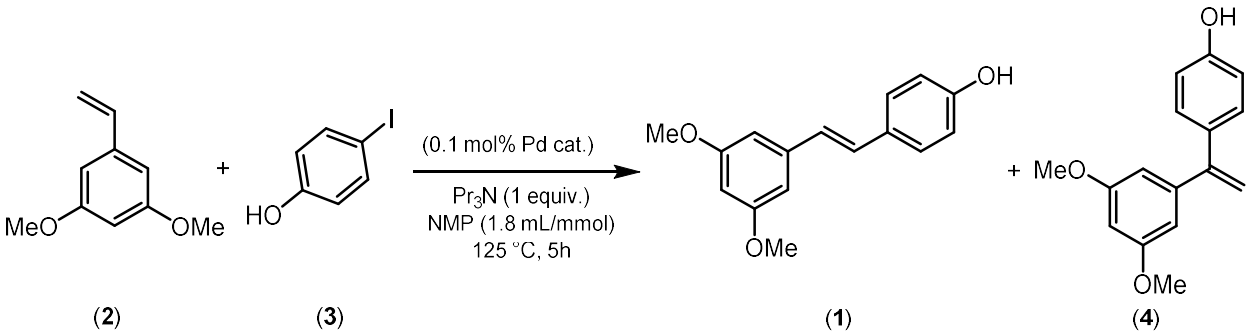
Pterostilbene (**1**)

In 2010 Cushman *et al*. used pathway A to synthesize a series of inhibitors of aromatase, using, in the case of **1**, high catalytic loading of Palladium Acetate and tetrabutylammonium bromide, with a global moderate yield (41%).[20] Afterwards Csuk *et al*. following pathway B, using 4-hydroxystyrene (**5**) and 3,5-dimethoxyiodobenzene (**6**) and Palladium Acetate (4.5 mol%) as a catalyst, still obtained the product in moderate yield (55%).[21] Excellent yields (97%) and acceptable regioisomeric ratio (100:9) were obtained by French et al. in 2011, which optimized the use of Dichlorobis(tricyclohexylphosphine)palladium.[22] Correia *et al*., instead used an Heck-Matsuda coupling with arenediazonium salts instead of aryl halides and triflates, obtaining a really good yield (85%).[23] In a very recent interesting example, reported by Barlow *et al*. Pterostilbene and other unsymmetrical stilbenes were synthesized by sequential Heck reactions of aryl bromides with ethylene.[24] Despite the important pharmacological properties of Pterostilbene and the several strategies described above, to obtain this molecule, as far as we know, there are still no studies with supported catalysts, neither on its transposition on continues flow reactors, with the aim to reach a more sustainable and green process.

RESULTS AND DISCUSSION

The synthesis of Pterostilbene, following the Mizoroki-Heck approach was tested for both the retrosynthetic strategies proposed in Scheme 1, with different supported catalysts, firstly in batch, to determine which conditions were more promising for a transposition of the synthesis in a continuous flow reactor. Following pathway A, we performed a first comparative screening of the most common commercially available palladium supported catalysts, in our best conditions, using 4-iodophenol (**3**), 3,5-dimethoxystryrene (**2**), tripropylamine (Pr_3N) as a base and N-methyl-2-pyrrolidone (NMP) as solvent (Table 1).

Table 1. Pathway A: Optimization of the coupling between (**2**) and (**3**), using different supported catalysts



(**2**) (**3**) (**1**) (**4**)

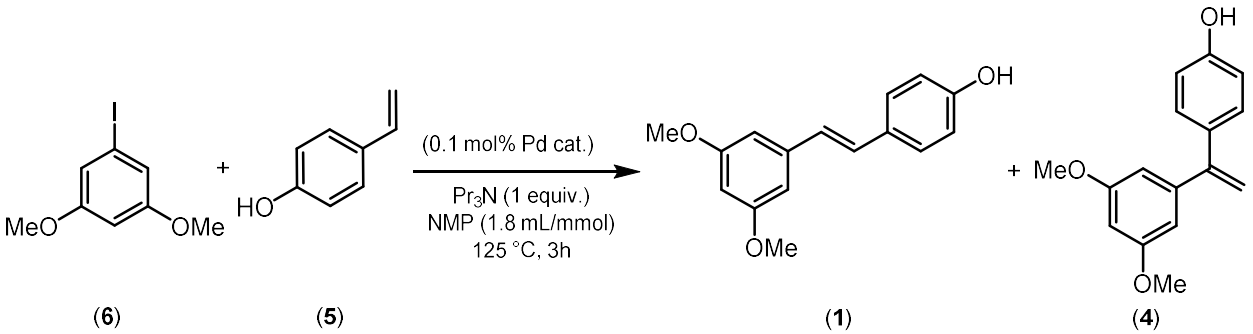
Entry[a]	Catalyst	Conv. of **1** %[b]	Conv. of **4** (%)[b]	TBAB (equiv.)	Time (h)	Yield %[c]
1	Fibre Cat 1007	77	18	-	5	-
2	PdEnCat 40	75	18	-	5	-
3	$Pd(PPh_3)_4$-PS	81	15	-	5	-
4	$PdCl_2(PPh_3)_2$-PS	63	14	-	5	-
5	FibreCat 1007	87	13	0.5	3	77
6	$Pd(PPh_3)_4$-PS	77	18	0.5	3	61

[a] General reaction conditions: 2 mmol of (**3**), 1 equiv. of P_3N, 2 equiv. of (**2**), 0.1 mol% of catalyst, 1.8 mL/mmol of NMP, 0 or 0.5 equiv. of TBAB, inert atmosphere, 125°C.
[b] Apparent conversion calculated by GC analysis as percentage ratio between the area of (**1**) or (**4**) and whole addition of the areas.
[c] Isolated yields of compound **1** were obtained after MPLC purification

The best conversions were obtained using FibreCat 1007 and $Pd(PPh_3)_4$-PS, which were therefore further investigated. Good results were also obtained using PdEnCat 40, but in our experience, the application of this catalyst in a flow reactor results in a higher leaching of Palladium.[25] To improve the reaction time and the regioselectivity of the reaction, we added sub-stoichiometric amounts of tetrabutylammonium bromide (TBAB), as suggested by the work of Jeffery.[26] The reaction was indeed faster and with a higher regioselectivity, as shown in entry 5 and 6 of Table 1.

Following pathway B, we initially tried to couple the free 4-hydroxystyrene (**5**), to 3,5-dimethoxyiodobenzene (**6**). Naturally, avoiding the use of protecting group for the hydroxy moiety, we would have increased the atom efficiency of the process, but results in terms of conversion and regioselectivity were not satisfactory, as shown in Table 2.

Table 2. Pathway B: Coupling between (**6**) and not-protected 4-hydroxystyrene (**5**) using different catalysts



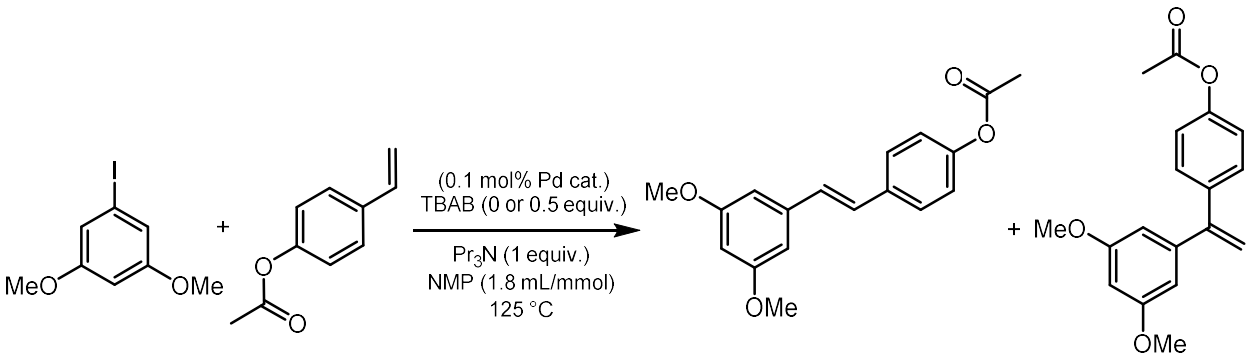
Entry[a]	Catalyst	Conv. of **1** %[b]	Conv. of **4** (%)[b]

1	Fibre Cat 1007	64	14
2	PdEnCat 40	64	14
3	$Pd(PPh_3)_4$-PS	68	13
4	$PdCl_2(PPh_3)_2$-PS	60	14

[a] General reaction conditions: 2 mmol of (**6**), 1 equiv. of P_3N, 2 equiv. of (**5**), 0.1 mol% of catalyst, 1.8 mL/mmol of NMP, inert atmosphere, 125°C, 5h.
[b] Apparent conversion calculated by GC analysis as percentage ratio between the area of (**1**) or (**4**) and whole addition of the areas.

The same reaction, performed using the protected 4-acetoxystyrene (**8**), was instead much more effective (Table 3), showing the importance of the protection on the hydroxy group, even though detrimental for atom economy, as we would need an additional saponification step. The best catalysts in terms of yield and selectivity resulted to be PdEnCat and $PdCl_2(PPh_3)_2$-PS. Anyway, they were all tested with additional TBAB showing not only better yields and selectivity, but a decrease of reaction time from 2 to 3 hours, as shown in Table 3.

Table 3. Pathway B: Optimization of the coupling between **6** and protected 4-acetoxystyrene (**8**) using different catalysts



(**6**) (**8**) (**9**) (**10**)

Entry[a]	Catalyst	Conv. of (**9**)%[b]	Conv. of (**4**)%[b]	TBAB (equiv.)	Time (h)	Yield %[c]
1	FibreCat 1007	80	10	-	3	53(46)
2	PdEnCat 40	89	9	-	3	81(72)
3	$Pd(PPh_3)_4$-PS	88	10	-	3	69(58)

4	$PdCl_2(PPh_3)_2$-PS	88	11	-	3	75(71)
5	FibreCat 1007	83	7	0.5	2	55(52)
6	PdEnCat 40	90	8	0.5	2	79(75)
7	$Pd(PPh_3)_4$-PS	93	7	0.5	2	87(81)
8	$PdCl_2(PPh_3)_2$-PS	90	9	0.5	2	77(72)

[a] General reaction conditions: 2 mmol of **6**, 1 equiv. of P_3N, 2 equiv. of **8**, 0.1 mol% of catalyst, 1.8 mL/mmol of NMP, inert atmosphere, 125°C, 3h
[b] Apparent conversion calculated by GC analysis as percentage ratio between the area of **9** or **10** and whole addition of the areas.
[c] GC yields calculated using Naphthalene as internal standard. In brackets the isolated yields of compound **9** after precipitation, as described in the experimental part.

Interestingly, the addition of TBAB drastically increased the activity of $Pd(PPh_3)_4$-PS, respect to all the other catalysts (entry 7, Table 3), with a regioselectivity of 93% and an isolated yield of 81%.

It was therefore interesting to optimize the minimal amount of TBAB needed, to preserve the positive effect in terms of yields and regioselectivity, and to avoid possible negative effects. In principle the presence of a quaternary ammonium salt, could affect negatively the efficiency of a flow reactor and drastically influence the leaching of Palladium from the supported catalyst.[27,28] As shown in Table 4, a good compromise is obtained using 0.20 equiv. of TBAB. Even supposing that no further purification was done on (**9**), the value of leached Palladium measured, would correspond to 5 ppm in the final product, which is acceptable for pharmacological application.

Table 4. Optimization of the coupling between **6** and **8**, respect to the amount of TBAB used and the corresponding leaching of Palladium

Entry[a]	TBAB (equiv.)	Conv. of (**9**)%[b]	Conv. of (**4**)%[b]	Yield %[c]	Leaching (%)

1	0.50	93	7	87(81)	1.0
2	**0.20**	**91**	**7**	**85(80)**	**0.9**
3	0.10	89	8	81(76)	-
4	0.05	72	6	-	-

[a] General reaction conditions: 2 mmol of **6**, 1 equiv. of P_3N, 2 equiv. of **8**, 0.1 mol% of $Pd(PPh_3)_4$-PS, 1.8 mL/mmol of NMP, inert atmosphere, 125°C, 1.5h
[b] Apparent conversion calculated by GC analysis as percentage ratio between the area of **9** or **4** and whole addition of the areas.
[c] GC yields calculated using Naphthalene as internal standard. In brackets the isolated yields of compound **9** after precipitation, as described in the experimental part.
[d] Calculated as percentage of Pd found in the reaction mixture at the end of the reaction, respect to the Palladium present in the supported catalyst.

It was also tested the possibility to re-cycle the catalyst ($Pd(PPh_3)_4$-PS), after filtration and washing, as described in the experimental part. However, as shown in Table 5, results for the second reaction were not satisfactory. It's worth to notice, that in this case, the results of the first reaction, run in the optimized conditions found previously, works even better, probably because we considerably increased the scale of the reaction, from 2 mmol to 12 mmol.

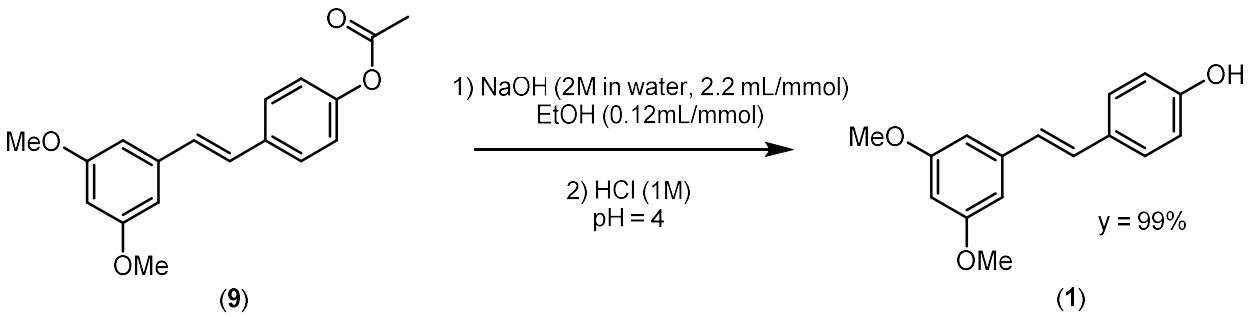
Table 5. Recycling of the catalyst

Entry	Time (h)	Conv. of (**9**)%[c]	Conv. of (**4**)%[c]	Yield %[d]
1[a]	1.5	92	8	90(86)
2[b]	3	67	6	65(61)

[a] General reaction conditions: 12 mmol of **6**, 1 equiv. of P_3N, 2 equiv. of **8**, 0.1 mol% of $Pd(PPh_3)_4$-PS, 1.8 mL/mmol of NMP, 0.2 equiv. of TBAB, inert atmosphere, 125°C.
[b] General reaction conditions: 6 mmol of **6**, 1 equiv. of P_3N, 2 equiv. of **8**, 0.1 mol% of $Pd(PPh_3)_4$-PS, 1.8 mL/mmol of NMP, 0.2 equiv. of TBAB, inert atmosphere, 125°C.
[c] Apparent conversion calculated by GC analysis as percentage ratio between the area of **9** or **4** and whole addition of the areas.
[d] GC yields calculated using Naphthalene as internal standard. In brackets the isolated yields of compound **9** after precipitation, as described in the experimental part.

Finally, to demonstrate the easy access to **1** from pathway B, product **9** was deprotected in basic condition using NaOH as a base, as described in the experimental part and depicted in Scheme 2, with a quantitative yield.

Scheme 2. Deprotection of the acetyl protecting group

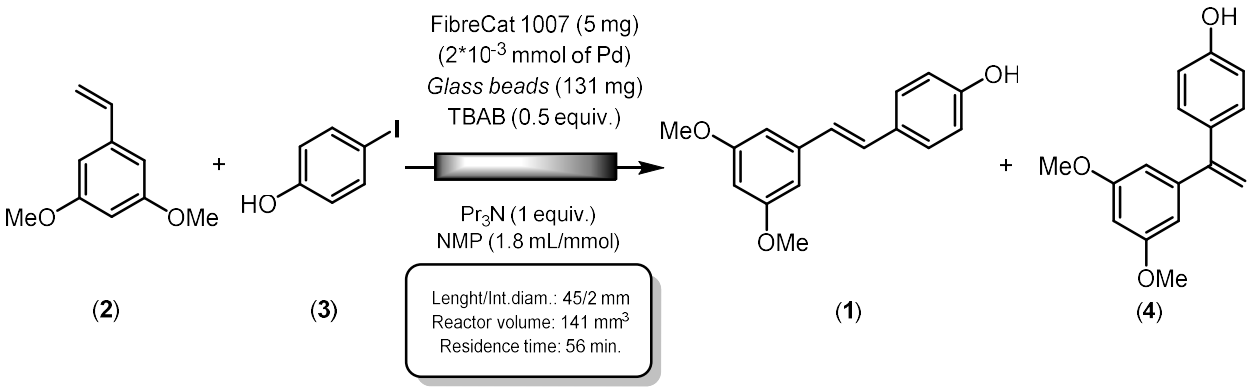


Comparing the results obtained on supported catalysts using pathway A and B, even though we increase the number of reaction steps, pathway B looks to be the most efficient.

The transposition of the synthesis of Pterostilbene in a continuous flow reactor has been tested consistently, following both the pathway proposed above, dispersing the catalyst in glass beads as inert material. Retrosynthetic pathway A was tested in the best conditions found (Table 1, Entry 5), using FibreCat 1007 as catalyst and 0.5 equiv. of TBAB, as shown in Table 6. entry 1-4, at 135°C and 0.15 mL/h of flow rate. Reaction proceeded with a poor conversion, as predictable from

the batch system, where reaction reached completion only after 3 hours, a reaction time above a suitable residence time for a flow reactor. In the attempt of increasing the conversion, we slightly changed reaction conditions, increasing temperature to 150°C and reducing the flow from 0.15 mL/h to 0.10 mL/h. As shown in Table 6 entry 5-9, even though conversion improved, it was still not satisfactory compared to the batch version of the reaction, and regioselectivity didn't improve.

Table 6. Transposition in continuous flow reactor of pathway A



Entry[a]	Fract.[b]	Volume (mL)[c]	**3** (mmol)[d]	Conv. (**1**)%[e]	Conv. (**4**)%[e]	Pd/**3** (mol%)[f]	Yield %[g]	*STY* (Kg/L*h)[h]
1	1	1.8	0.75	58	8	-	-	-
2	2	0.6	0.25	56	8	-	-	-
3	3	1.6	0.67	52	9	-	-	-
4	4	1.2	0.50	40	9	-	-	-
	Overall	5.2	2.17	52	9	0.09	-	-
5	1	0.3	0.13	64	8	-	-	-
6	2	1.6	0.67	65	9	-	-	-

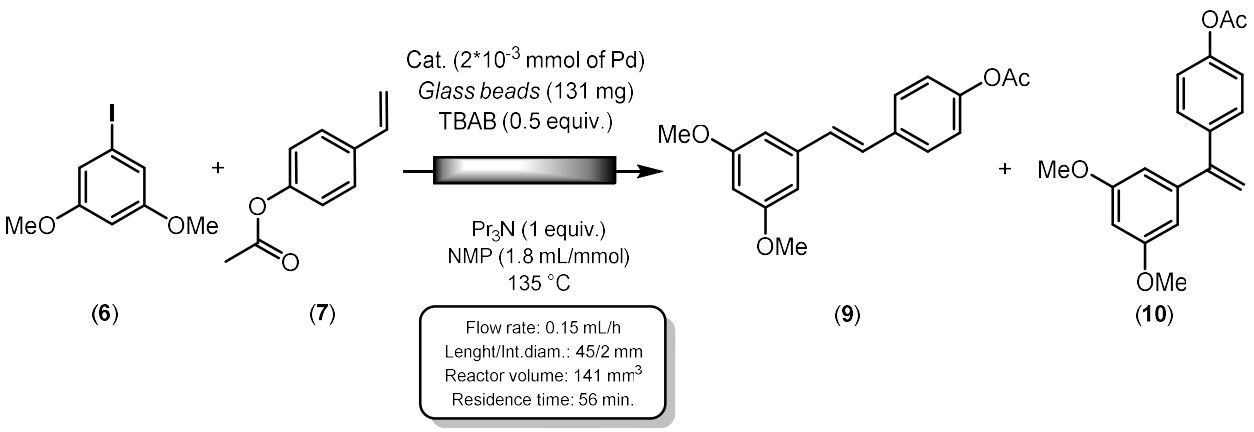
7	3	2.5	1.04	62	10	-	-	-
8	4	0.7	0.29	61	10	-	-	-
9	5	1.7	0.71	51	10	-	-	-
	Overall	6.7	2.79	61	10	0.07	50	1.72

[a] Entries 1-4: T = 135°C, flow rate = 0.15 mL/h. Entries 5-6: T = 150°C, flow rate = 0.10 mL/h
[b] General reaction conditions: 2 mmol of **3**, 1 equiv. Pr_3N, 2 equiv. of **2**, 1.8 mL/mmol NMP, 0.5 equiv. of TBAB, 5.2 mL of mixture overall volume.
[c] Volume of the collected fractions
[d] Amount of **3** initially present in the analyzed fraction
[e] Conversion evaluated through glc as ratio between the area of the product and the sum of all the areas
[f] Ratio between the amount of Pd in the reactor and the amount of **3** eluted
[g] GC yield calculated using naphthalene as internal standard
[h] Space-Time Yield obtained as Kg of product on volume of the reactor during residence time

Pathway A showed overall poor results, especially in terms of isolated yields, therefore was not taken into consideration for a real synthetic application.

Regarding pathway B, we initially transferred in flow our best conditions obtained in batch, initially without the use of TBAB, with PdEnCat 40 as catalyst (Table 3, entry 2), but the low conversion obtained, around 40%, convinced us to don't pursue this way. We therefore continued with the adding of 0.5 equiv. of TBAB, using PdEnCat 40 and $Pd(PPh_3)_4$-PS as catalysts as shown in Table 7.

Table 7. Transposition in continuous flow reactor of pathway B



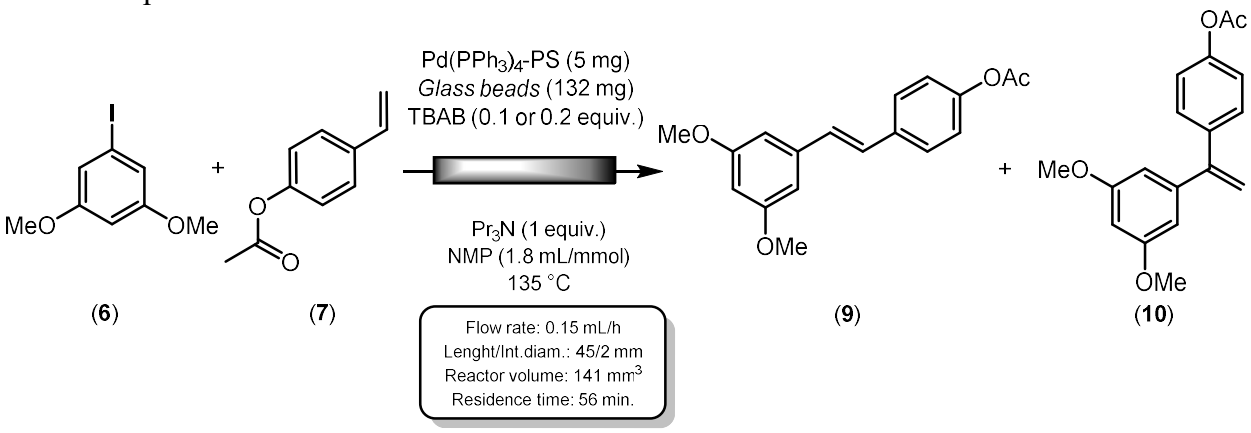
Entry	Catalyst	Fract.[a]	Volume (mL)[b]	**6** (mmol)[c]	Conv. (**9**)%[d]	Conv. (**10**)%[d]	Pd/**6** (mol%)[e]	Yield %[f]
1	PdEnCat 40	1	2.1	0.81	82	6	-	-
2		2	0.9	0.35	78	5	-	-
3		3	2.7	1.04	70	5	-	-
		Overall	5.6	2.15	72	5	0.09	51(48)
4	$Pd(PPh_3)_4$-PS	1	0.1	0.04	89	8	-	-
5		2	1.7	0.65	86	8	-	-
6		3	0.6	0.23	85	7	-	-
7		4	2.4	0.92	84	7	-	-
8		5	0.6	0.23	82	7	-	-
9		6	0.5	0.19	83	7	-	-
10		7	2.0	0.77	78	7	-	-
		Overall	7.8	3.00	83	7	0.07	72(67)

[a] General reaction conditions: 2 mmol of **6**, 1 equiv. Pr3N, 2 equiv. of **7**, 1.8 mL/mmol NMP, 0.5 equiv. of TBAB, 5.2 mL of mixture overall volume.
[b] Volume of the collected fractions
[c] Amount of 6 initially present in the analyzed fraction
[d] Conversion evaluated through glc as ratio between the area of the product and the sum of all the areas
[e] Ratio between the amount of Pd in the reactor and the amount of **6** eluted
[f] GC yield calculated using naphthalene as internal standard

There is a clear improvement respect to pathway A in terms of conversions, yield and regioselectivity. Moreover, the system showed a longer lifetime respect to the same reaction in

batch. Afterwards, for the optimization of reaction conditions, we used $Pd(PPh_3)_4$-PS, which showed a better catalytic activity and we looked for the minimal amount necessary of TBAB to run efficiently the reaction. As Shown in Table 8, we tested 0.1 equiv. of TBAB (Entries 1-6) and 0.2 equiv. of TBAB (Entries 7-13), which resulted to be a good compromise between yield and reactor lifetime. In the best conditions found (Table 8, Entries 7-13), we obtained similar conversion and yield to the static reactor in batch, formally recycling the catalyst two times. This result is rather interesting if compared with the poor results obtained initially to recycle the catalyst in batch (Table 5).

Table 8. Optimization of TBAB amount in continuous flow reactor



Entry[a]	Fract.[b]	Volume (mL)[c]	**6** (mmol)[d]	Conv. (**9**)%[e]	Conv. (**10**)%[e]	Pd/**6** (mol%)[f]	Yield %[g]	*STY* (Kg/L*h)[h]
1	1	1.8	0.69	81	10	-	-	-

2	2	0.5	0.19	80	9	-	-	-
3	3	2.7	1.04	78	9	-	-	-
4	4	0.7	0.27	78	9	-	-	-
5	5	2.2	0.85	74	9	-	-	-
6	6	5.6	2.15	66	8	-	-	-
	Overall	13.5	5.19	71	9	0.04	61(57)	5.61
7	1	1.8	0.69	89	10	-	-	
8	2	0.5	0.19	87	10	-	-	
9	3	2.4	0.92	86	9	-	-	
10	4	1.0	0.38	85	9	-	-	
11	5	1.9	0.73	84	9	-	-	
12	6	2.3	0.88	85	9	-	-	
13	7	4.5	1.73	80	8	-	-	
	Overall	14.4	5.54	84	9	0.04	75(72)	8.79

[a] Entries 1-6: 0.1 equiv. of TBAB. Entries 7-13: 0.2 equiv. of TBAB
[b] General reaction conditions: 2 mmol of **6**, 1 equiv. Pr3N, 2 equiv. of **7**, 1.8 mL/mmol NMP, 0.5 equiv. of TBAB, 5.2 mL of mixture overall volume.
[c] Volume of the collected fractions
[d] Amount of **6** initially present in the analyzed fraction
[e] Conversion evaluated through glc as ratio between the area of the product and the sum of all the areas
[f] Ratio between the amount of Pd in the reactor and the amount of **6** eluted
[g] GC yield calculated using naphthalene as internal standard
[h] Space-Time Yield obtained as Kg of product on volume of the reactor during residence time

To verify the reproducibility of the optimized system and to determined on a reaction crude the amount of Palladium leached, we run the reaction another time, with the results reported in Table 9. The amount of Palladium found is lower than the corresponding leached in the batch reaction (Table 4), and below the suggested residual amount for direct biomedical application.[29]

Table 9. Reproducibility of the reaction and Palladium leaching analysis

Entry[a]	Fract.	Volume (mL)[b]	**6** (mmol)[c]	Conv. (**9**)%[d]	Conv. (**10**)%[d]	Pd/**6** (mol%)[e]	Leaching (%)[f]

1	1	1.8	0.69	87	10	-	-
2	2	2.9	1.12	84	9	-	-
3	3	3.0	1.15	84	9	-	-
4	4	3.0	1.15	83	9	-	-
5	5	3.8	1.46	79	8	-	-
	Overall	14.4	5.54	82	9	0.04	0.5

[a] General reaction conditions: 2 mmol of **6**, 1 equiv. Pr_3N, 2 equiv. of **7**, 1.8 mL/mmol NMP, 0.2 equiv. of TBAB, 5.2 mL of mixture overall volume.
[b] Volume of the collected fractions
[c] Amount of **6** initially present in the analyzed fraction
[d] Conversion evaluated through glc as ratio between the area of the product and the sum of all the areas
[e] Ratio between the amount of Pd in the reactor and the amount of **6** eluted
[f] Calculated as ratio between the Pd found in the reaction mixture and the Pd present in the initial catalyst

In conclusion, it was shown that the synthesis of Pterostilbene can be readily performed through Mizoroki-Heck reaction using supported-catalysts, and that the transposition to continuous flow reactor can be conveniently achieved in optimized conditions.

EXPERIMENTAL SECTION

General information

All reagents and solvents were used as received, without further purification, unless stated otherwise. Reagents and solvents were bought from Sigma Aldrich and kept under argon atmosphere, when needed. All the reactions were performed under Ar atmosphere, unless stated otherwise. When necessary, anhydrification was performed by heating the glassware with a hot-gun, followed by vacuum-argon cycles. All the supported catalysts were purchased by Sigma Aldrich and manipulated under air. The palladium content for each catalyst used was: PdEnCat 40 (0.42 mmol/g); FibreCat 1007 (0.72 mmol/g); $PdCl_2(PPh_3)_2$-PS (1.01 mmol/g); $Pd(PPh_3)_4$-PS

(0.70 mmol/g). All capillary tubing and microfluidic fittings were purchased from IDEX Health & Science. Gas tight syringes were purchased from SGE. Syringe pumps were purchased from New Era model N300. Product isolation was performed in an MPLC system (Buchi Pump Module C-601, equipped with a differential refractometer Jasco RI 4030), using silica (40-63 μm, Sigma) or manually. TLC analysis was performed using Silica on aluminum foils TLC plates (F254, Merck 60) with visualization under ultraviolet light (254 nm and 365 nm). ^{1}H (600MHz) and ^{13}C (133MHz) spectra were recorded on ambient temperature using a Varian INOVA 600 MHz. Known products were characterized by comparing to the corresponding 1H NMR and 13C NMR from literature. All the reactions were followed via GC-MS, performed on a GC-MS combination (Agilent 6890 Network GC System coupled to a Mass Spectrometer; Agilent 5973 Network Mass Selective Detector), while GC-FID analysis were performed on a DANI GC 1000. Melting points were determined with a Kofler Reichert-Jung and are uncorrected. Leaching anaylsis were performed via ICP-OES Spectro Genesis (Spectro Analitical Instrument).

Synthesis of Precursors

3,5-Dimethoxystyrene (**2**)

In a two-necked round-bottom flask, equipped with a dropping funnel and magnetic stirrer, dried and put under inert atmosphere, methyltriphenylphosphonium bromide (14.4 g, 39.8 mmol) and anhydrous THF (60 mL) were added. The mixture was stirred for 30 minutes, then cooled at -78 °C. A solution of 3,5-dimethoxybenzaldehyde (5.00 g, 30.1 mmol) in anhydrous THF (30 mL) was added dropwise, then the mixture was allowed to warm to room temperature. The mixture was quenched with methanol (10 mL), dried under reduced pressure and filtered in a plug of silica (Hexane : Et_2O 94:6), to obtain the desired product (4.85g, 99%) as a colorless oil. $^{1}HNMR$ (600

MHz, $CDCl_3$), δ: 6.66 (dd, J = 17.4, 10.8 Hz, 1H), 6.58 (d, J = 2.3 Hz, 1H), 6.39 (t, J = 2.3 Hz, 1H), 5.73 (d, J = 17.4 Hz, 1H), 5.26 (d, J = 10.8 Hz,1H), 3.82 (s, 6H) ppm.

4-Hydroxystyrene (**5**)

In a two-necked round-bottom flask 4-acetoxystyrene (2.00 g, 12.4 mmol), KOH (1.70 g, 30.3 mmol) and water (180 mL) were added. The mixture was stirred at 0 °C for 1 hour. Acetic acid was added to quench the reaction and the reaction mixture was extracted with ethyl acetate (3 x 10 mL). The organic phase was washed with brine, dried with sodium sulfate and evaporated under reduced pressure to obtain the desired product (5, 1.48 g, 99%) as a white solid. ^{1}HNMR (600 MHz, CDCl 3), δ: 7.31 (dd, J = 8.5 Hz, 2H), 6.79 (d, J = 8.6 Hz, 2H), 6.71-6.61 (dd, J = 17.6, 10.7 Hz, 1H), 5.52 (d, J = 17.5 Hz, 1H), 5.13 (d, J = 10.8 Hz, 1H), 4.72 (s, 1H) ppm.

3,5-Dimethoxyiodobenzene (**6**)

In a two-necked round-bottom flask, equipped with a reflux condenser and magnetic stirrer, dried and kept under inert atmosphere, 3,5-dimethoxy-bromobenzene (8.00 g, 36 mmol), sodium iodide (10.8 g, 72.0 mmol), copper iodide (0.344g, 1.80 mmol), N,N'-dimethylethylendiamine (0.400 mL, 3.60 mmol) and anhydrous dioxane (30 mL) were added. Argon was bubbled through the mixture for 10 minutes, then the reaction was left at 110 °C overnight. Next, the mixture was allowed to cool at room temperature, quenched with ammonia (30% in water, 20 mL), and poured in water (75 mL). The water phase was extracted with CH_2Cl_2 (3 x 30 mL) and the organic phase was dried with sodium sulfate and evaporated under reduced pressure to obtain the desired product

as a white solid (6, 8.84 g, 96%). M.p.: 74-75°C (lit. 74-75°C). ^{1}H-NMR (600 MHz, $CDCl_3$), δ: 6.84 (d, J = 2.2 Hz, 1H), 6.39 (s, 1H), 3.74 (s, 6H) ppm.

General procedure for the synthesis of Pterostilbene (1) in batch reactors

Path A

In a two-necked round-bottom flask, equipped with a reflux condenser and magnetic stirrer, dried and put under inert atmosphere, the supported catalyst (0.002 mmol of Pd), 3,5-dimethoxystyrene (2, 0.490 mL, 4.00 mmol), 4-iodophenol (3, 0.440 g, 2.00 mmol), and TBAB (0.322 g, 1.00 mmol), tripropylamine (0.380 mL, 2.00 mmol) and N-methyl-2-pyrrolidone (3.6 mL) were added. The reaction mixture was warmed up at 125°C. After full conversion, the reaction was quenched with saturated NH_4Cl in water (5 mL) and the reaction was poured in water and extracted with ethyl acetate when purification was required. The collected organic phase was dried with sodium sulfate and the product was isolated with MPLC (Hexane : Et_2O 48:52) to obtain a white solid.

Pterostilbene (**1**)

M.p.: 85°C (Lit. 88°C)4. ^{1}HNMR (600 MHz, $CDCl_3$) δ: 7.40 (d, J = 8.5 Hz, 2H), 7.02 (d, J = 16.2 Hz, 1H), 6.89 (d, J = 16.2 Hz, 1H), 6.82 (d, J = 8.5 Hz, 2H), 6.64 (d, J = 2.0 Hz, 2H), 6.37 (t, J = 2.0 Hz, 1H), 3.82 (s, 6H) ppm. E/Z ratio = 99:1 Spectroscopic data in agreement with literature.

4-(1-(3,5-dimethoxyphenyl)vinyl)phenol (**4**)

^{1}HNMR (600 MHz, $CDCl_3$) δ: 7.22 (d, J = 8.6 Hz, 2H), 6.78 (d, J = 8.5 Hz, 2H), 6.49 (d, J = 2.2 Hz, 2H), 6.43 (t, J = 2.1 Hz, 1H), 5.35 (d, J = 20.5 Hz, 2H), 3.76 (s, 6H). ppm. Elemental Analysis: C16 H16O3 (P.M. = 256,30): Calculated C% 74.98, H% 6.29; Measured C% 75.01, H% 6.23.

Path B

In a two-necked round-bottom flask, equipped with a reflux condenser and magnetic stirrer, dried and put under inert atmosphere, the supported catalyst (0.002 mmol of Pd), 3,5-dimethoxyiodobenzene (6, 0.528 g, 2.00 mmol), styrene (5 or 8, 4.00 mmol), and TBAB (quantity specified in Table 3 and Table 4 in the main paper), tripropylamine (0.380 mL, 2.00 mmol) and N-methyl-2-pyrrolidone (3.6 mL) were added. The reaction mixture was warmed up at 125°C. After full conversion, the reaction was quenched with saturated NH_4Cl in water (5 mL) and the reaction was poured in water and extracted with ethyl acetate when purification was required. The collected organic phase was dried with sodium sulfate. The GC yield was measured with naphthalene as internal standard and the product was isolated with MPLC (Hexane : Et_2O 8:2) or precipitation (H_2O : MeOH 1:1 and filtration) to obtain a white solid.

4-(3,5-dimethoxystyryl)phenyl acetate (**9**)

M.p.: 128-130°C (Lit. 128°C). ^{1}HNMR (600 MHz, $CDCl_3$), δ: 7.50 (d, J = 8.5 Hz, 2H), 7.08 (d, J = 8.5 Hz, 2H), 7.06 (d, J = 16.5 Hz, 1H), 6.98 (d, J = 16.2 Hz, 1H), 6.66 (d, J = 2.0 Hz, 2H), 6.40 (t, J = 1.8 Hz, 1H), 3.83 (s, 6H), 2.30 (s, 3H) ppm. E/Z ratio = 97:3. Spectroscopic data in agreement with literature.

Saponification of the 4-(3,5-dimethoxystyryl)phenyl acetate

In a two-necked round-bottom flask, equipped with a reflux condenser and magnetic stirrer, 9 (1.0 g, 3.40 mmol), NaOH (2 M in water, 7.5 mL) and ethanol (0.41 mL) were added. The mixture was

heated at 80 °C under mixing for one hour. Next, HCl (1 M in water, 10 mL) was added and the desired product was filtered as a white off solid and washed with water (**1**, 0.859 g, 99%).

Catalyst recycle

In a two-necked round-bottom flask, equipped with a reflux condenser and magnetic stirrer, put under inert atmosphere $Pd(PPh_3)_4$-PS (30 mg, $12*10^{-3}$ mmol Pd), 3,5-dimethoxyiodobenzene (**6**, 3.168 g, 12.0 mmol), 4-acetoxystyrene (**8**, 3.66 mL, 24.0 mmol), and TBAB (0.774 g, 2.40 mmol), tripropylamine (2.28 mL, 12.00 mmol) and N-methyl-2-pyrrolidone (21.6 mL) were added. The reaction mixture was warmed up at 125°C. After 2 hours the reaction mixture was filtered and the recovered catalyst was washed with water (3 x 5 mL) and ethyl acetate (3 x 5 mL), recovering 27 mg of catalyst that were dried under vacuum. The filtered reaction mixture was quenched with saturated NH_4Cl in water (15 mL) and the reaction was poured in water and extracted with ethyl acetate (3 x 20 mL). The collected organic phase was dried with sodium sulfate and evaporated under reduced pressure. The product was isolated via precipitation (1:1 H_2O:MeOH, 40 mL) and filtration to obtain **9** as a white solid (3.07 g, 86%). The reaction was then repeated with the recycled catalyst at half of the scale, obtaining after 3 hour the desired product with the same method in 61% isolated yield.

General procedure for the synthesis of Pterostilbene (1) and 4-(3,5-dimethoxystyryl)phenyl acetate in continuous flow reactors

Preparation of packed bed reactors

The reactors were prepared with PTFE tubes (2 mm ID, 3 mm OD, 8 cm long), and it was packed with the supported catalyst mixed with glass beads (100-212 μm, Sigma Aldrich cat. G1145) 1:25

w/w. The composition of the packed bed reaction and its length was specified for every experiment in the main paper. Every reactor was initially capped on one side with 0.5 cm of glassy wool, then on the other side the mixture of glassy beads and the catalyst was introduced into the reactor dry, then packed with the solvent chosen for the reaction a 2 atm of pressure. The reactor was finally capped on the other side in the same way. The reactor is then submerged in a warm oil bath, before starting the flow reaction. Regarding the system connection, the reactor was connected to the inlet and the outlet via PEEK nut 1/4”28, while the inlet is connected to the syringe (Model 1010 TLL Waters SYR – Hamilton, 10 mL) via Luer Lock connection.

General procedure for flow reactions

In one schlenk tube, 4.00 mmol of halide (3 or 6), 8.00 mmol of styrene (2 or 7), 4.00 mmol of tripropylamine (0.760 mL), TBAB (0.1-0.5 equiv.) and N-methyl-2-pyrrolidone (7.2 mL) were added. The stock solution was then transferred in the syringe and placed in the syringe pump and connected to the setup. The flow rate was set according to article, and all the collected fractions, after the work up similar to the batch reactions, were analyzed by GC-MS or GC-FID, then the isolated yields were determined or the leaching test were conducted.

Leaching measurement

Regarding the measurement of palladium leaching, the reaction mixtures of batch reactions were filtered on a fritted glass filter, while flow reaction mixtures were manipulated directly. The crudes were calcinated in a porcelain crucibles with 8 addition of acqua regia at high temperature (8 x 5 mL). The crude was heated up until dryness and cooled down to room temperature. The residue was then solubilized with milliq water (3 x 1 mL) transferred in a 5 mL volumetric flask and made up to the mark. These sample were analyzed via ICP-OES.

ASSOCIATED CONTENT

Supporting Information.

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ABBREVIATIONS

TBAB, tetrabutylammonium bromide; NMP, N-methyl-2-pyrrolidone; Pr_3N, tripropylamine; GC, Gaschromatography.

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