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Aerobic waste-minimized Pd-catalysed C–H alkenylation in GVL using a tube-in-tube heterogeneous flow reactor⁺

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Herein we report the design and application of a tube-in-tube packed-bed flow reactor for the first time for the development of a heterogeneous palladium catalysed oxidative C–C bond formation process. In particular, we have defined an innovative tube-in-tube protocol for the Fujiwara–Moritani C–H alkenylation reaction in biomass-derived γ -valerolactone. Thanks to this novel flow system, the oxidative C–H activation process has been conducted using a sub-stoichiometric amount of an external organic oxidant (benzoquinone) in the presence of molecular oxygen as a benign sacrificial oxidant. The protocol features very limited metal leaching and high stability of the catalyst over time. In this study, the applicability of the protocol to a range of substituted acetanilides and *N*-methoxybenzamides and various electron-poor alkenes has been demonstrated. The practical utility of the tube-in-tube reactor has also been proved by performing the flow methodology on a multi-gram scale.

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Introduction

Molecular oxygen can be considered among the most ideal and greenest oxidants. O_2 is abundant and readily available, has a low molecular weight and generally generates only water as an environmentally friendly by-product. In recent years, the demand for greener and more sustainable synthesis methods has generated a great interest in the use of O_2 as a reagent.¹ In fact, it can be very efficient to conduct not only oxidation processes, but also transition-metal mediated redox reactions which are among the most challenging to perform in a regioand stereo-selective manner, particularly on a large scale. Recently, the use of microreactors for the liquid-phase catalytic transformation mediated by oxygen has been receiving growing attention,² highlighting the possibility to use flow technologies to efficiently deliver gaseous oxygen into a reaction mixture.

In this area, tube-in-tube flow conditions have proved to be a very useful tool to develop effective synthesis procedures.³ Pioneering studies on the use of tube-in-tube flow reactors were conducted in 2010 by Ley and co-workers who applied this technology in the ozonolysis of alkene in continuousflow eventually succeeding in improving the safety hazard associated with the formation of ozonide and peroxide intermediates. $\!\!\!^4$

Tube-in-tube apparatus consist of two concentric hoses. Generally, a gaseous reagent is applied at a modulated pressure in the outer tube, while the reaction mixture is flowed through the inner tube made of gas permeable polytetrafluoroethylene (AF-2400). The intuitive advantage of this technology is that it allows an easier and solid approach for those reactions requiring the use of gaseous reagents with additional increased safety of the process.⁵ Indeed, the confinement of a pressurized gas in small microreactor volumes reduces the hazards associated with high-pressure conditions and promotes rapid interphase mixing, thus improving massand thermal transfer. Additionally, Ley's introduction of the tube-in-tube technology is a unique method that can allow us to possibly realize a "non-stop" flow protocol in the presence of gaseous reagents with an intimate contact between the reaction mixture and the gas for the entire residence time.^{6,7}

For these reasons, to date, a plethora of synthesis methodologies have been developed exploiting the tube-in-tube configuration including hydrogenation, oxidation, and general catalytic C–N/C–O bond formation.⁸ The latter received particular attention due to the possibility of performing consecutive oxidative catalytic pathways in the presence of oxygen as a final sacrificial oxidant. The consequent minimization or elimination of stoichiometric amounts of an additional oxidant (metal or organic) represents a very interesting feature with water as the only by-product. To date, a limited number of protocols based on the use of heterogeneous catalysts have been

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performed in a tube-in-tube reactor system. One example is the olefin metathesis⁹ where the tube-in-tube approach is utilized to facilitate the removal of the ethylene by-product leading to an improved yield and selectivity. The heterogeneous catalytic three-phase hydrogenation reaction has also been conducted using a tube-in-tube flow system to pre-saturate the mixture with the gaseous reagent and then subsequently let the reaction proceed in a regular packed column.¹⁰ The heterogeneous oxidation of benzyl alcohol has also been accomplished¹¹ by packing a solid catalyst inside the reactor and improving the process safety.

In the case of an oxygen tube-in-tube flow system, the final goal is also to reach the sufficiently high reactivity to reduce or eliminate the use of an additional external oxidant.

In the realm of oxidative catalytic C–C bond formation, tube-in-tube flow reactors have been utilized successfully but only in the presence of a homogeneous catalytic system while the challenging use of a heterogeneous catalyst still represents a major limitation for applying the tube-in-tube technology.

Heterogeneous recyclable catalysts are extremely interesting as it has been proved that they can be repeatedly recovered and reused with consistent identical catalytic efficiency. In addition, they can help simplify the work-up procedures once easily separated from the reaction mixture leading to an advance in terms of sustainability and waste minimization.¹²

The combination of the tube-in-tube technology with heterogeneous catalysis can therefore be an effective innovative tool to minimize the use of stoichiometric oxidants while succeeding in the use of recoverable catalysts. Ideally, this approach is even more effective if performed in a safer reaction medium.¹³ In this regard, the use of biomass derived solvents is rapidly gaining importance in organic chemistry,¹⁴ and among those, γ -valerolactone (GVL), a derivative of lignocellulosic biomass, has demonstrated remarkable potential as a substitute for the widely used dipolar aprotic solvents, such as DMF, DMAc, or NMP.¹⁵ In a few cases, the use of GVL in place of common solvents resulted in additional desirable effects, such as reduced metal-leaching from heterogeneous palladium catalysts and improved catalyst recyclability.¹⁶

Oxidative alkenylation of arenes is a useful C–H functionalization methodology known as the Fujiwara–Moritani reaction.¹⁷ This reaction, discovered in the early 1970s, was initially performed using homogeneous Pd sources and stoichiometric or over-stoichiometric amounts of an oxidant.¹⁷ Further improvements over the years have led not only to the use of O_2 as the final oxidant in the presence of homogeneous catalysts but also to the use of a heterogeneous catalyst in combination with a stoichiometric amount of an organic or inorganic oxidant.¹⁸ So far, due to the difficulty of efficiently using heterogeneous catalytic systems in combination with oxygen as a sacrificial oxidant (Scheme 1), it has never been reported the greenest.

As a part of our research on the development of sustainable flow technologies in combination with heterogeneous catalytic systems and bio-derived reaction media, we report in this contribution our results on the definition of the first oxidative



Scheme 1 Features of the Fujiwara–Moritani reaction to date.

C–C bond formation performed in a tube-in-tube packed bed flow reactor operated in GVL as an environmentally friendly reaction medium. In particular, we have focused our study on the oxidative alkenylation of substituted acetanilides and *N*-methoxybenzamides.

Results and discussion

We started our investigation by considering the previous studies reported in the literature where to perform a Fujiwara– Moritani reaction, an organic or metal oxidant was used to regenerate the palladium(II) species responsible for the catalytic alkenylation process (Scheme 2).

In the particular case where benzoquinone (BQ) is used, the redox cycle includes the palladium catalyst oxidation by benzoquinone that is in turn reduced to the corresponding hydro-



Scheme 2 Features of the packed-bed tube-in-tube flow protocol.



Scheme 3 Redox catalytic cycle for the envisaged oxidative C-H alkenylation.

quinone (HQ) (Scheme 3).^{15c} We have investigated the conditions under which molecular oxygen can be used to reoxidize hydroquinone, therefore allowing its use as an additive with an oxygen terminal oxidant in flow (Scheme 3).

We investigated the C–H alkenylation between acetanilide **1a** and butyl acrylate **2a** as the representative process catalysed by heterogeneous Pd/C. It is noteworthy that by simply applying oxygen pressure (1–8 bar) to a flow-reactor packed with the heterogeneous palladium catalyst, ^{15c} products are formed only in traces (Scheme 2).

When benzoquinone is added in a sub-stoichiometric amount, conversion of **1a** to **3a** is observed but it only depends on the amount of the organic oxidant. Therefore, under these conditions, molecular oxygen is not able to re-oxidize benzoquinone acting as a final sacrificial oxidant. This is expectedly due to the fact that oxygen under simple flow conditions is not effectively transferred into the heterogeneous reaction mixture. Therefore, as planned, the adoption of the tube-in-tube technology can be crucial to furnish a suitable solution to conduct this process in continuous-flow.

To prove this hypothesis, we assembled a customized flow tube-in-tube test reactor (see the ESI[†]) and screened various parameters such as the diameter of the inner tube, length of the reactor and back pressure regulator (BPR).

The inner tube has been charged with Pd/C catalyst (10% w/w) and the test reactions have been conducted on a 2.5 mmol scale of acetanilide **1a**. As standard conditions we used a sub-stoichiometric amount of BQ (20 mol%) and 1 eq. of *para*-toluenesulfonic acid (*p*-TsOH). As previously reported,^{18a} this acid is effective in facilitating the C-H metalation process by increasing the electrophilicity of the intermediate Pd(II) species.

The results reported in Table 1 first of all prove that the tube-in-tube approach is effective and conversion of **1a** is higher than the amount of benzoquinone used (20%) proving that the re-oxidation of hydroquinone by oxygen is possible under these conditions. Anyway, the internal tube is very delicate and breaks easily, limiting the use of larger oxygen pressure values. An AF-2400 tubing with 1.59 or 3.18 mm internal diameter breaks easily when oxygen pressure increases (BPR set to 8.2 bar). A maximum of 68% conversion to **3a** could be achieved but with not reproducible operating times due to the frequent breaking of the tubing. Finally, the AF-2400 tubing with 0.79 mm internal diameter (1/32")

Table 1 Screening of flow system parameters^a



Entry	O ₂ (bar)	BPR (bar)	ID internal tube (mm)	Residence time (min)	C^{b} [%]
1	1	_	1.59	45	12
2	2	2.1	1.59	80	23
3	4	5.2	1.59	100	68
4	4	8.2	1.59	—	c
5	3	3.5	0.79	90	66
6	5	8.2	3.18		<i>c</i>
7	5	5.2	3.18	90	64
8	5	5.2	0.79	120	70
9	5	5.2	0.79	120	72^d
10	5	5.2	1.59		<i>c</i>
11	4	5.2	0.79	95	68

^{*a*} Reaction conditions: **1a** (2.5 mmol), **2a** (3.75 mmol), Pd/C 10% w/w (60 mg), GVL [0.5 M] unless otherwise stated, flow rate 10 μ L min⁻¹, 150 cm reactor length; the flow reactor is installed in a thermostat box at 85° C. ^{*b*} GLC conversion has been determined using samples of pure compound as reference standards; the remaining materials are **1a** and **2a**. ^{*c*} The inner tube easily breaks. ^{*d*} GVL 0.2 M.

showed the best performance in terms of flexibility and stability also at higher pressures of oxygen (Table 1, entries 8–10). This tube led to 72% conversion to product **3a** in 2 h of residence time with 5 bar of oxygen pressure and a BPR of 5.2 bar. Further optimizations were then conducted using the 0.79 internal diameter tubing by varying the length of the reactor and the flow rate (Table 2).

As expected, decreasing the length of the reactor did not produce good results in terms of conversion to product while optimal conversions of 77% were achieved using a 2 m reactor

Table 2 Optimization of the flow rate and the residence time^a



1	10	100	100	55
2	15	200	140	77
3	15	250	155	77
4	20	100	57	34
5	20	200	95	52
6	20	250	110	68
7	50	250	70	43

^{*a*} Reaction conditions: **1a** (2.5 mmol), **2a** (3.75 mmol), Pd/C 10% w/w (60 mg), GVL [0.2 M]; the flow reactor is installed in a thermostat box at 85° C. ^{*b*} GLC conversion has been determined using samples of pure compound as reference standards; the remaining materials are **1a** and **2a**.

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and a flow rate of 15 μ L min⁻¹. Importantly, the reaction afforded selectively the *ortho*-alkenylated acetanilide **3a** in 2.2 h of residence time with no observation of any other byproduct. To our delight, under these conditions, 75% of isolated yield was achieved highlighting the optimal selectivity of the reaction and compared to batch, the flow conditions were more effective in preserving the product stability. It is also worthy to note that considering the product yield and the excess of reagent **2a**, the carbon utilization between reagents and products is 61%. It is also worthy to mention that a further increase of reactor length led to no conversion improvement.

At this stage, with the optimized flow set-up and parameters, we tested the possibility to further reduce the amount of *p*-benzoquinone used to steer the process. To our delight, we observed that, under otherwise identical conditions, using 10 or 7.5 mol% of *p*-benzoquinone led to almost comparable results. When only 5 mol% of *p*-benzoquinone was used, the conversion slightly decreased, while with 2.5 mol% or by removing the organic oxidant, the conversion decreased to 47% and 20% respectively (Table 3).

Based on this optimization, we then tested the reactor by continuously pumping the reaction mixture for a representative 8 h (Scheme 4). Stable conversion was achieved leading to a productivity of 0.42 mmol h^{-1} of *ortho*-alkenylated acetanilide **3a**, with a TON value of 137.5 and a TOF of 17.2 h^{-1} .

To gain more insight into the performance of the flow reactor, we have measured the amount of palladium leached into the GVL solution by MP-AES (Fig. 1). This analysis revealed very limited metal leaching from the heterogeneous support (0.2–0.02 ppm) which is almost one order of magnitude lower than the best performance reported in the literature nowadays for similar reaction conditions.

GVL confirms to be not only a greener solvent but also a more effective alternative to classic DMF being able to minimize the palladium leaching as proved by the comparison of GVL and DMF tested in the same experimental set-up.

Table 3 Optimization of the benzoquinone amount in the flow system^a



^{*a*} Reaction conditions: **1a** (2.5 mmol), **2a** (3.75 mmol), Pd/C 10% w/w (60 mg), GVL [0.2 M]; the flow reactor is installed in a thermostat box at 85° C. ^{*b*} GLC conversion has been determined using samples of pure compound as reference standards; the remaining materials are **1a** and **2a**. ^{*c*} Isolated yield is given parentheses.



Scheme 4 Large scale C-H alkenylation between acetanilide 1a and alkene 2a.



Fig. 1 Conversion to 3a and palladium leaching over operating hours.

The newly designed flow reactor and the optimized flow conditions were used to explore the scope of oxidative C-H alkenylation using a variety of substituted acetanilides **1a–f** and alkenes **2a–f** (Scheme 5). Gratifyingly, the envisaged mono-alkenylation occurred selectively in the *ortho*-position of acetanilides in the reaction with *n*-butylacrylate as an electron-poor alkene. Substituted acetanilides were also good substrates, affording products mono-alkenylated at the *ortho*-position of the acetamido-group, confirming their excellent ability in directing the C-H activation processes. Importantly, the presence of halide substituents on the aromatic substrate is well tolerated (**3b**, **3c** and **3d**), which allows further orthogonal functionalisation through classical cross-coupling processes. In all the cases, the expected products were obtained in good to excellent yields, without notable formation of side products.

Further exploration of the substrate scope proceeded with N-methoxy-benzamide (4a–c) (Scheme 5). These substrates have been very rarely explored while they are interesting as they enable preparation of the isoindolinone ring *via* a consecutive C–H alkenylation/cyclization process. The methodology herein reported indeed is the first example exploiting the reactivity of N-methoxy-benzamides in the presence of a heterogeneous palladium catalyst and an environmentally friendly bio-based reaction medium in a continuous flow fashion. The reaction proceeds with the initial selective C–H olefination forming the *E*-isomer which undergoes the aza-Wacker annulation. Methyl substitution both *para* and *meta* to the *N*-methoxy benzamido



Scheme 5 Scope of tube-in-tube packed bed flow C–H alkenylation. Reaction conditions: **1a** (2.5 mmol), **2a** (3.75 mmol), residence time: 200 min; the flow reactor is installed in a thermostat box at 85° C. GLC conversion is given in parentheses.

group gave almost identical results in the reactions with *n*-butylacrylate (respectively **5a** and **5b**). The presence of the methoxy group showed a slightly better isolated yield (**5c**).

After establishing the feasibility and solidity of the tube-intube oxidative flow system, the scope was expanded both for acetanilides and N-methoxybenzamide by testing the suitability of different electron poor olefins (3g, 3h and 5d, 5e). In addition, high yields were also achieved by reacting unsubstituted acetanilide with acrylonitrile (3i) and styrene (3j). Finally, the broad-spectrum applicability of the tube-in-tube flow process was tested by reacting acetanilide with maleimide (3k) opening also the possibility to achieve complex API intermediates in a straightforward manner. It is worthy to note the results obtained with maleimide. This compound is very sensitive to basic conditions where fast hydrolysis of the cyclic imides can occur. It is not trivial to perform its alkenylation using more classic reaction conditions in the presence of bases as in the Mizoroki-Heck reaction. Notably, in order to have better comprehension of the influence of the reduced amount of the oxidant additive we performed all the reactions

using either 10 mol% or 20 mol% of *p*-benzoquinone (Scheme 5 and ESI† respectively). The isolates were in most of the cases comparable. This suggests the efficiency of our tube-in-tube flow reactor that allows us to define an effective trust-worthy protocol.

To fully exploit the combination of the tube-in-tube technology with the use of a heterogeneous catalyst and the bioderived solvent (GVL), we have also optimized the work-up procedure. The reaction mixture collected at the output of the flow reactor was distilled using a Kugelrohr apparatus to recover 95% of the GVL mass which, after checking its purity by NMR, was reused for further flow reactions. The crude dried mixture, containing *p*-TsOH, benzoquinone and the product, was directly subjected to column chromatography to afford pure products. These steps led to a very low calculated E-factor value of 3.

To better appreciate the results obtained, the E-factor value calculated for our protocol has also been compared to those calculated for other representative and/or recent works on the oxidative C–H alkenylation of acetanilides involving the use of either palladium- or rhodium-catalytic systems in combination with a variety of terminal oxidants.

Looking at the results reported in Scheme 6, the first evidence is that the medium employed for the reaction (blue diagrams) and the solvents used for the work-up procedures expectedly strongly affect the E-factor values. Adoption of diluted conditions, no reclaiming of the solvents and, depending both on the catalyst and on the oxidant used, the need for several extraction cycles with water/solvents to isolate the crude reaction mixture, also contribute to the final E-factor values.

The analysis in Scheme 6 shows also that in terms of mass involved, the oxidant accounts for a small part of the waste generated. However, the amount of additional oxidant used influenced the final composition of the reaction mixture and the subsequent simplicity of its purification. The presence of organic and/or inorganic oxidants affected the quality rather than the quantity of waste to a greater extent. For this reason, the use of molecular oxygen is preferable as it generates only water as waste.

In addition, a further analysis has been conducted by comparing the process using Reaction Mass Efficiency (RME) and Materials Recovery Parameter (MRP) (Table 4) as additional metrics. These values improve when the mass of the reagent decreases (use of low molecular weight oxidant or molecular oxygen) or when any mass is recovered at the end of the reaction (solvent reclaim and catalyst recovery). This analysis indeed gives a more immediate comprehension of the benefit exploited from the process herein developed. It is possible to appreciate that, in most of the literature processes considered, RME is below 6%, and in the worst cases, it is below 1%. These values implicate that even if the isolated yields are high, the ratio between the product recovered and the total input mass is very low. Consequently, the MRP in which also the stoichiometry factor between the acetanilide and the acrylate is considered is low. On the other hand, for our flow protocol herein developed, a carefully designed synergy of different



Scheme 6 E-factor profile distribution. (a) ref. 18a; (b) ref. 18b; (c) ref. 18c; (d) ref. 18c in the presence of air; (e) ref. 18d; (f) ref. 18e; (g) ref. 18f using ball-milling under solvent-free conditions; (h) ref. 18g; (i) ref. 15c; (k) ref. 15c under flow conditions; and (l) this work.

Table 4 RME and MRP analysis^a

Yield	RME	MRP
85%	2.4%	0.027
85%	4.9%	0.083
98%	5.7%	0.071
97%	6.1%	0.077
76%	0.6%	0.012
82%	4.1%	0.084
71%	0.1%	0.001
91%	1.9%	0.023
80%	0.1%	0.002
95%	2.5%	0.027
97%	3.2%	0.035
75%	25.8%	0.428
	Yield 85% 98% 97% 76% 82% 71% 91% 80% 95% 97% 75%	Yield RME 85% 2.4% 85% 4.9% 98% 5.7% 97% 6.1% 76% 0.6% 82% 4.1% 71% 0.1% 91% 1.9% 80% 0.1% 95% 2.5% 97% 3.2% 75% 25.8%

 a Details of the calculation are provided in the ESI.† b Under aerobic conditions. c Using flow conditions.

methodological aspects together with the implementation of the heterogeneous tube-in-tube reactor as an effective tool to deliver O_2 into the reaction mixture led to a genuine sustainable process. Indeed, an E-factor reduction of 25–200% and very good performance in terms of RME and MRP have been obtained.

Conclusions

In conclusion, we have herein reported the challenging assembly of a packed-bed tube-in-tube flow reactor exploiting for the first time its ability in the Fujiwara–Moritani type C–H alkenylation reaction of acetanilides and benzamides catalysed by heterogeneous Pd/C in biomass-derived GVL as the reaction medium. The *ortho*-functionalized products are obtained in good yields, and the flow set-up allows us to establish a good rate of re-oxidation for the catalytic system used guaranteeing durable flow conditions. The packed-bed flow reactor showed good performance in terms of gram-scale reaction and very limited leaching of metal in solution leading to a productivity of 0.42 mmol h^{-1} . A detailed analysis of the factor that contributes to the overall E-factor has been conducted together with the analysis of other metrics such as RME and MRP in order to assess the improvement in terms of sustainability of the reported flow protocol.

Conflicts of interest

There are no conflicts to declare.

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