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A Continuous Flow Solution to Achieving Efficient Aerobic Anti-Markovnikov Wacker Oxidation

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Abstract: An aerobic anti-Markovnikov Wacker oxidation for the flow-synthesis of arylacetaldehydes is reported. In the process, flow chemistry techniques have provided a means to control and minimise the over-oxidation of sensitive products. The reaction showed general applicability to various functionalised styrenes and provided a process capable of a multi-gram scale.

Keywords: aerobic Wacker oxidation; gas-liquid flow; microreactors; palladium catalysis; tube-in-tube

The use of molecular oxygen as a reagent for the synthesis of organic compounds is an attractive research subject and of particular interest to industry. Molecular oxygen is inexpensive, readily available and a suitable green alternative for many oxidising agents currently employed in synthesis.[1] The use of oxygen often requires transition metal catalysts in order to promote the rate of reaction and in the majority of cases the desired transformations can be achieved with high conversion. However, in cases requiring the partial oxidation of compounds, over-oxidation can be a significant problem and one which is more easily controlled by employing alternative oxidants.

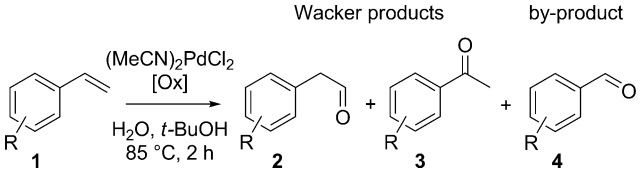
One such process, brought to our attention by a paper from Grubbs and co-workers,[2] involves the anti-Markovnikov Wacker oxidation of styrenes to sensitive arylacetaldehyde products wherein the use of sterically hindered *tert*-butyl alcohol as reaction solvent accounts for the excellent aldehyde selectivity. To prevent over-oxidation of the desired products at the benzylic position, ultimately leading to cleavage of the olefinic bond to form benzaldehydes, copper and oxygen which are traditionally employed in the Wacker oxidation[3] were substituted for bezoquinone (BQ) since the stoichiometry can be more easily controlled.

Several avenues towards achieving an anti-Markovnikov Wacker oxidation have previously been investigated. The use of directing groups[4] has been employed but substrate scope is limited somewhat. Another insight by Spencer and co-workers[5] showed that an increase from catalytic to stoichiometric $PdCl_2$ shifts the selectivity in favour of aldehyde products. Furthermore, the use of *t*-BuOH to achieve the desired anti-Markovnikov product was first demonstrated by Feringa and co-workers.[6] using a catalyst comprised of $(MeCN)_2PdClNO_2$ and $CuCl_2$ with O_2. However, less than 10% yield was reported for the oxidation of styrene to phenylacetaldehyde.

Given our group's experience with flow chemistry techniques[7] and in particular with gas-flow devices,[8] we envisioned developing an efficient aerobic anti-Markovnikov Wacker oxidation. Through proper application of microreactors and more precise control of reaction parameters, such as oxygen pressure, reaction time and temperature, it is conceivable that any amount of over-oxidation, when using $CuCl_2$ and O_2, may be sufficiently mitigated, a problem which has hitherto prevented the development of such an aerobic process.

We initiated our investigation by comparing BQ and $CuCl_2$ with O_2 in batch mode (Table 1). When using BQ as oxidant 4-chlorostyrene gave almost full conversion and good selectivity as previously reported,[2] although some over-oxidation was also observed (entry 1). The more electron-rich 4-methoxystyrene gave a lower conversion and a poorer selectivity for the arylacetaldehyde (entry 2). Again, some over-oxidation was observed but to a lesser extent with the electron-rich derivative. Substituting BQ for $CuCl_2$ (5 mol%) and O_2 (10 bar) led to complete conversion of both electronically varying examples. However, as expected, significantly increased over-oxidation of the desired products to the corresponding benzaldehydes was observed.[9] Decreasing the oxygen pressure

Table 1. Anti-Markovnikov Wacker oxidation of various functionalized styrenes in batch mode.[a]



Entry	R	[Ox]	Amount	Conv.[b] [%]	Selec.[b] (**2**/**3**/**4**)
1	4-Cl	BQ	1.15 equiv.	94	84:3:7
2	4-OMe	BQ	1.15 equiv.	75	66:6:3
3	4-Cl	$CuCl_2+O_2$	5 mol%	99	70:5:24
4	4-OMe	$CuCl_2+O_2$	5 mol%	99	67:4:28
5	4-OMe	$CuCl_2+O_2$	1 mol%	98	79:7:12

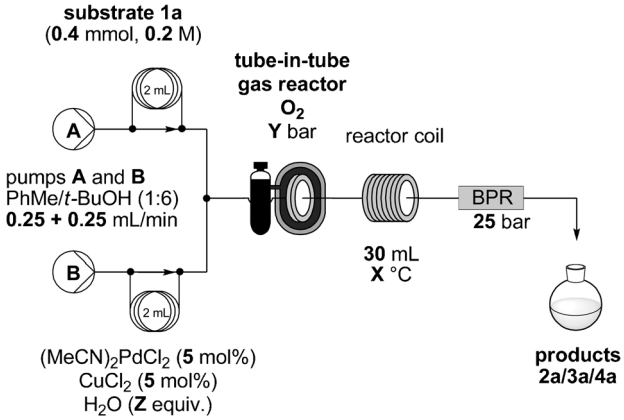
[a] *Reaction conditions:* substrate (1.25 mmol), $(MeCN)_2PdCl_2$ (2.5 mol%), H_2O (1.1 equiv.), *t*-BuOH (10 mL), O_2 (10 bar), 85 °C, 1 h. A stainless steel autoclave ($v=50$ mL) was used.
[b] Ratio of products **2**:**3**:**4** determined by GC analysis.

(5 bar) led to both incomplete conversion and continued formation of the respective benzaldehydes, possibly due to the competing rate of over-oxidation leading to oxygen depletion within the autoclave. However, it was possible to reduce the extent of over-oxidation by reducing the co-catalyst loading five-fold to 1 mol% (entry 5, Table 1). Further decreasing the co-catalyst loading resulted in longer reactions times.

It is also important to note that stirred-tank autoclaves that exist in the pharmaceutical industry can be used to perform aerobic oxidation with dilute air mixtures (5–8% O_2 in N_2) requiring a constant flow of gas through the reactor to prevent oxygen depletion.[1d] Therefore, despite small improvements in the aerobic batch process, further batch optimisations would be of little relavance and a flow-mode process was quickly pursued.

The reaction was found to proceed rapidly with $CuCl_2$ and O_2 giving reaction times of approximately 15 min using 5 mol% catalyst loadings allowing for extensive reaction optimisations in a short time frame. We began by addressing which co-solvent would be appropriate to prevent *t*-BuOH freezing in the flow tubes and pumps at room temperature. A mixture of PhMe/*t*-BuOH (1:6) gave the best results compared to other co-solvents which caused the formation of other by-products. Following this the catalyst loadings of palladium and copper were briefly investigated and a catalyst loading of [Pd]/[Cu] (5 mol%/5 mol%) was found to give good conversions and selectivities while allowing for some variation in reaction time and oxygen pressure to obtain the best results for specific substrates.

The flow set-up used for the optimisation experiments is shown in Scheme 1. A substrate solution containing 4-methoxystyrene **1a** (0.4 mmol, 0.2 M) was loaded into injection loop **A** and a catalyst solution containing $(MeCN)_2PdCl_2$, $CuCl_2$ and H_2O was



Scheme 1. *Reaction conditions:* PhMe/*t*-BuOH (1:6), flow rates ($0.25+0.25$ mL min^{-1}), reaction coil ($v=30$ mL), gas reactor ($v=0.7$ mL) AF2400 ($l=1.5$ m). Injection loop A (2 mL): substrate **1a** (0.4 mmol, 0.2 M). Injection loop B (2 mL): $(MeCN)_2PdCl_2$, $CuCl_2$, H_2O.

loaded into injection loop **B**. A Uniqsis FlowSyn reactor was used to pump the reagents through the inner tube of a tube-in-tube gas reactor pressurised with pure oxygen. The reaction stream was then passed through a 30-mL stainless steel reaction coil maintained at constant temperature, after which the reaction stream passed through a 25-bar back-pressure regulator (BPR). This was required to maintain a homogeneous solution by preventing out-gassing of oxygen at pressures up to 25 bar. Finally, the exiting product stream is collected in a small vial under a constant flow of nitrogen to remove excess oxygen.

The conditions for the anti-Markovnikov Wacker oxidation of 4-methoxystyrene **1a** were varied with respect to temperature (Figure 1, **A**), H_2O equivalents (Figure 1, **B**) and pressure of pure oxygen (Figure 1, **C**). Catalyst loadings, solvent mixture and the resi-

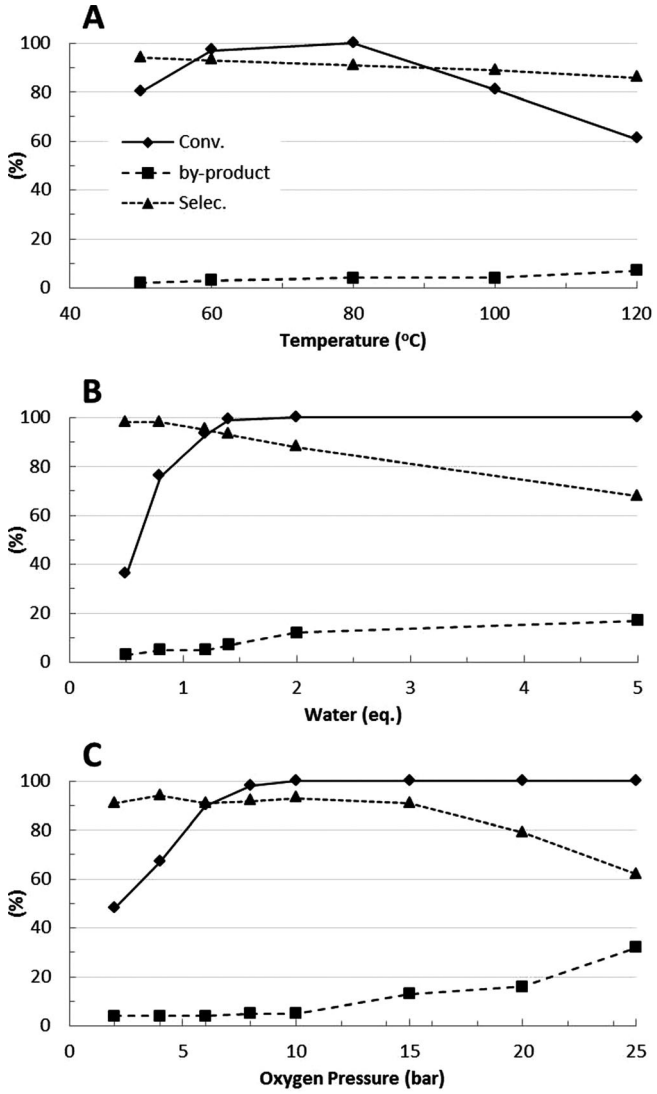


Figure 1. The effect of varying parameters on selectivity and by-product formation. (**A**) Temperature: H_2O (2 equiv.), O_2 (10 bar). (**B**) H_2O equivalents: $T = 80\,°C$, O_2 (10 bar). (**C**) Oxygen pressure: H_2O (1.4 equiv.), $T = 60\,°C$. *General reaction conditions:* PhMe/*t*-BuOH (1:6), flow rates (0.25 + 0.25 mL min^{-1}), reaction coil (stainless steel, $v = 30$ mL), gas reactor ($v = 0.7$ mL) AF2400 ($l = 1.5$ m). Injection loop A (2 mL): 4-vinylanisole **1a** (0.4 mmol). Injection loop B (2 mL): $(MeCN)_2PdCl_2$ (5 mol%), $CuCl_2$ (5 mol), H_2O (X equiv.).

dence time (*via* flow rate) remained constant throughout these optimisations.

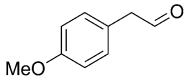
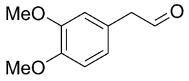
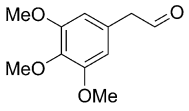
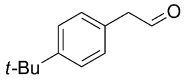
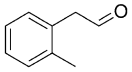
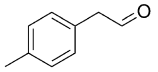
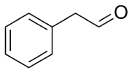
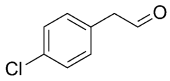
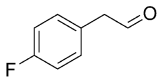
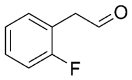
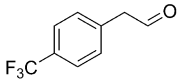
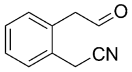
The reaction temperature was first studied (Figure 1, **A**). A relatively low temperature of 50 °C led to better selectivities and less by-product formation before full conversion could be reached in the desired 1-h residence time frame. Increasing the temperature progressively led to an increased reaction rate and full conversion with good selectivity and minimal by-product formation at an optimal 60 °C. This was followed by a drop-off in reaction rate and selectivity above 80 °C. Following this, the equivalents of water were investigated (Figure 1, **B**). Since trace amounts of water in the *t*-BuOH used in these reactions could contribute to the reaction, sub-stoichiometric amounts of water were also investigated. Incomplete conversion of the starting material was observed within the 1-h residence time frame up until the addition of 1.2 equiv. of water. However, given the ease which with residence time can be controlled using flow we considered 1.4 equiv. as optimum for the overall reaction rate and to avoid incomplete conversion when varying the substrates. Next we studied the influence of oxygen pressure on the reaction (Figure 1, **C**). At a constant combined flow rate (0.5 mL min^{-1}) through the gas reactor, complete conversion was not observed until an oxygen pressure of 8 bar was applied. Further increasing the pressure of oxygen resulted in significant over-oxidation and degradation of the reaction selectivity. Gas burette measurements determined the oxygen concentration at 8 bar to be 0.097 M, not surprisingly close to the 0.1 M reaction concentration. This demonstrates nicely the ease and accuracy with which controlling the oxygen concentration using flow-technologies enables reactions that would prove particularly challenging in batch-mode.

As a means of isolating and purifying the arylacetaldehyde products we chose to crystallize them as the bisulfite adducts.[10] This was only possible due to the relatively pure product stream. The product fraction was collected directly from the reactor into a stirred beaker of sodium bisulfite solution in EtOH/H_2O leading to preferential crystallisation of the arylacetaldehyde sulfite adduct.

The isolated yields reported in Table 2 are based on the recovery of arylacetaldehyde sulfite adduct crystals by vacuum filtration. The free aldehyde can be regenerated from the bisulfite adduct in the normal way, by addition of aqueous sodium bicarbonate, or under non-aqueous conditions by addition of chlorotrimethylsilane.[10c]

With optimised conditions in hand for the aldehyde selective anti-Markovnikov Wacker oxidation of **1a** and a simple, efficient means of isolation, we investigated the reaction with a variety of functionalised styrenes, shown in Table 2, using the same flow set-up used in Scheme 1. Not surprisingly, the electronic properties of the aryl substituents significantly affect the selectivities and the propensity for over-oxidation. Electron-rich styrenes gave slightly worse selectivity with more of the methyl ketone being formed in contrast to substrates bearing halogen substituents which preferred formation of the desired arylacetaldehyde products. However, the electron-rich species had less of a tendency to over-oxidise before complete conversion was reached. For example; the reaction of 4-(trifluoromethyl)styrene **1k** formed significant amounts

Table 2. Anti-Markovnikov Wacker oxidation of various functionalized styrenes.[a]

Entry	Arylacetaldehyde **2**	Selec.[b] (**2**/**3**/**4**)	Yield[c] [%]
a		83:7:7	74
b		77:13:7	75
c		82:6:11	78
d		82:3:12	72[d]
e		92:2:3	56
f		88:4:4	77
g		79:6:8	66
h		84:4:11	80
i		82:4:9	80
j[e]		88:2:6	77
k[f]		77:2:14	59
l		84:3:3	80[d]

[a] *Reaction conditions:* substrate (0.4 mmol, 0.2 M), $(MeCN)_2PdCl_2$ (5 mol%), $CuCl_2$ (5 mol%), H_2O (1.4 equiv.), solvent = PhMe/*t*-BuOH (1:6), flow rates ($0.25+0.25$ mL min^{-1}), residence time = 60 min, gas reactor ($v=0.7$ mL) AF2400 ($l=1.5$ m), O_2 ($p=8$ bar), reaction coil (stainless steel, $v=30$ mL), $T=60$ °C.
[b] Product ratios add up to the overall conversion and were determined by GC analysis of the crude product mixture.
[c] Isolated yields are based on the recovery of arylacetaldehyde sulfite adduct crystals.
[d] Isolated yield after column chromatography.
[e] A residence time of 75 min was used.
[f] A residence time of 40 min was used.

of by-product before all of the starting material had been consumed. Therefore, reducing the residence time led to lower conversion and lower by-product formation thereby improving the overall yield. Substrates **1e** and **1j** with *ortho* substituents both gave excellent selectivity and less by-product formation. However, despite the high conversions to desired products for this process, the crystallisation of some products proved more difficult, particularly due to the small scale of the crystallisation process. Those examples with *ortho* substituents proved particularly difficult to recover using this technique.

Using the reaction concentration and conditions optimised up to this stage in the investigation, 0.4 mmol of substrate is typically employed using the injection loop system. To demonstrate the scalability of this process we planned to increase the throughput and run the reaction continuously for several hours. A second optimisation of conditions was necessary to find the optimum oxygen pressure at the higher substrate concentration. (Table 3). Initial attempts to increase the reaction concentration to 0.5 M led to palladium black precipitation (entry 1). This did not cause the reactor to block, however the concentration was subsequently decreased to 0.3 M for the following experiments as a precautionary measure.

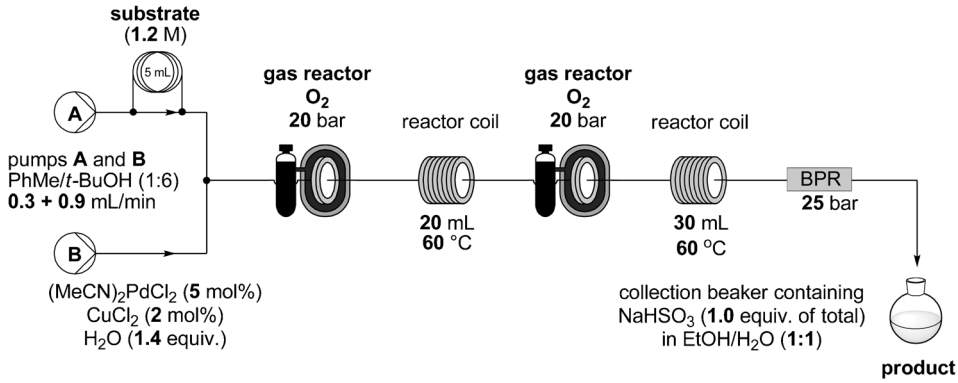
Somewhat surprisingly, significant amounts of both unreacted starting material and over-oxidised by-product were observed together, similar to the observation made when lowering the oxygen pressure in the batch autoclave. Lowering the co-catalyst loading to 1 mol% (entry 3) decreased the rate of competing over-oxidation and gave almost full conversion.

When increasing the reaction concentration back to 0.5 M palladium black formation was no longer a problem, however, oxygen depletion continued to prevent

Table 3. Selected optimisation experiments for scale up.[a]

Entry	Conc. [M]	[Pd]:[Cu] [mol%]	O_2 [bar]	Conv.[b] [%]	Selec.[b] (**2**/**3**/**4**)
1[c]	0.5	5:5	10	37	20:4:13
2	0.3	5:5	15	79	49:5:25
3	0.3	5:1	20	98	69:11:18
4	0.5	5:1	20	73	50:7:16
5	0.5	5:1	30	95	64:10:21
6[d]	0.5	5:1	20+20	74	49:5:20
7[d]	0.5	5:2	20+20	94	64:15:15
8[d]	0.3	5:2	20+20	99	70:6:23
9[d,e]	0.3	5:2	20+20	99	76:4:19

[a] *Reaction conditions:* substrate **1h**, $(MeCN)_2PdCl_2$, $CuCl_2$, H_2O (1.4 equiv.), solvent = PhMe/*t*BuOH (1:6), flow rates ($0.25+0.25$ mL min^{-1}), residence time = 60 min, gas reactor ($v=0.7$ mL) AF2400 ($l=1.5$ m), O_2 ($p=$ X bar), reaction coil (stainless steel, $v=30$ mL), $T=60$ °C.
[b] Conversions and product ratios were determined by GC analysis of the crude product mixture.
[c] Palladium black was observed.
[d] Flow set-up as used in Scheme 2 using a 5-mL injection loop for substrate, flow rates of $0.2+0.6$ mL min^{-1} were used with the catalyst stream being pumped continuously giving a combined reaction plug volume of 20 mL.
[e] A flow rate of $0.3+0.9$ mL min^{-1} was used.



Scheme 2. Flow scheme for multi-gram preparation of **2h** utilising a second gas-reactor to provide adequate oxygen supply. The 5-mL injection loop was used during optimisations but not during the scale-up process whereby reagents were introduced continuously through the pumps.

full conversion from being reached. A similar problem encountered in our group involving hydrogen depletion was solved by introducing a second gas reactor into the set-up.[8f] We decided therefore to investigate a similar set-up in this process.

The effect of double dosing the reaction stream with oxygen (Scheme 2) showed some improvements in favour of the desired product (entry 6). Oxygen depletion continued to hinder the reactions progress at high concentration (entry 7) and increasing oxygen pressures further only led to unacceptable over-oxidation. Using a 0.3 M reaction concentration allowed for 99% conversion and increasing the combined flow rate to 1.2 mL min^{-1} (40 min residence time) eventually provided acceptable conditions for scale-up (entry 9).

The overall continuous throughput of the reaction was increased from 3 mmol h^{-1} using the set-up in Scheme 1 to 21.6 mmol h^{-1} using the set-up in Scheme 2 and optimised scale-up conditions (entry 9, Table 3). In total 96 mmol of substrate **1h** were processed over the course of a 6-hour run period (allowing for collection of all material contained within the reactor and dispersion effects). The exiting product stream was collected into a large stirred beaker containing sodium bisulfite solution and the resulting crystals were collected by vacuum filtration at the end of the experiment. An overall isolated yield of 71% yield (17.62 g, 68 mmol) for the pure crystalline 4-chlorophenylacetaldehyde sulfite adduct of **2h** with a selectivity of 76:4 (**2h/3h**) for the crude product mixture was achieved.

In conclusion, we have developed an efficient and reproducible, aerobic, flow synthesis for arylacetaldehydes from functionalized styrenes. Only through the application of flow technologies such as the tube-in-tube gas reactor was it possible to accurately charge a reaction stream with a stoichiometric amount of gaseous oxygen. In addition, the relative purity of the product stream allowed for simple, selective, crystallization of the desired products by formation of the bisulfite adducts. This aerobic oxidation is applicable to both electron-rich and electron-poor styrenes. In addition, the removal of spent oxidants such as hydroquinone or metal based oxidants by expensive separation techniques is not necessary. Furthermore, the use of a tube-in-tube gas reactor to charge a pressurised reaction stream with only the necessary volume of pure oxygen improves the safety of such a process in flow. No effective reactor headspace prevents the combination of solvent and oxygen in the gas-phase to form explosive mixtures, lessening chances of auto-ignition. Additionally, with no incentive to use diluted oxygen mixtures; lower, safer reactor pressures can be employed to obtain the same oxygen concentrations in solution.

Scalability of the process was tested when oxygen depletion at the higher reaction concentrations became a problem. However, rapid optimisations and employment of a double gas-reactor set-up allowed us to obtain similar reaction selectivities with over 7 times the initial throughput and subsequently led to successful synthesis on a multi-gram scale.

Experimental Section

Batch Mode Synthesis of Arylacetaldehydes from Styrenes

Oxidant *p*-benzoquinone (1.15 equiv.) and catalyst $(MeCN)_2PdCl_2$ (2.5 mol%) were added to *t*-BuOH (10 mL) which was heated to 85 °C. Olefin (1.25 mmol) and H_2O (1.1 equiv.) were then added to the reaction mixture (0.125 M) and stirred for 60 min at 85 °C. Alternatively, *p*-benzoquinone was replaced with $CuCl_2$ (5 mol%) and the reaction vessel was pressurised with pure O_2 (10 bar). After 60 min the reaction vessel was rapidly cooled in ice water and depressurised. A sample was immediately taken for GC analysis.

Flow Mode Synthesis of Arylacetaldehydes from Styrenes

Olefin (0.4 mmol) was dissolved in PhMe/*t*-BuOH (1:6, 2 mL, 0.2 M) and loaded into injection loop A (2 mL). $(MeCN)_2PdCl_2$ (5 mol%), $CuCl_2$ (5 mol%) and H_2O (1.4 equiv.) were dissolved in PhMe/*t*-BuOH (1:6, 2 mL) and loaded into injection loop B (2 mL). The reagents were pumped using a Uniqsis Flowsyn reactor *via* the 2-mL PEEK injection loops A and B at a flow rate of 0.25 + 0.25 mL min^{-1} [using PhMe/*t*-BuOH (1:6) as stock solvent] through a T-piece mixer which combines the two streams. The reaction mixture then flowed through a tube-in-tube gas reactor ($v = 0.7$ mL) AF2400 ($l = 1.5$ m) pressurised with pure O_2 (8 bar) followed by a 30-mL stainless steel reaction coil at 60 °C (residence time: 60 min). The exiting product stream passed through a BPR (15 bar) and a 6 mL fraction (containing the reaction plug and any dispersion) was collected into a vial (flushed with nitrogen) containing $NaHSO_3$ (0.4 mmol) dissolved in H_2O/EtOH (1:1, 1 mL). Crystallisation of the arylacetaldehyde sulfite adduct occurs slowly over the time that the fraction was collected (12 min). (Further dilution of the product fraction with EtOH sometimes helped to encourage crystallisation if necessary.) The adduct crystals were collected by Buchner filtration, washed with EtOH followed by Et_2O and finally dried under vacuum. A small sample can be collected for GC analysis to determine conversions and selectivities before addition to the sodium sulfite solution.

Acknowledgements

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