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Continuous flow/waste-minimized synthesis of benzoxazoles catalysed by heterogeneous manganese systems†

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Herein, we present our results on the development of a waste minimized protocol for the synthesis of 2-arylbenzoxazoles in continuous flow. Manganese-based heterogeneous catalysts were used in combination with cyclopentylmethyl ether as an environmentally friendly and safe reaction medium. The use of oxygen promotes the oxidative process ensuring at the same time a complete regeneration of the catalyst adopting a flow configuration which does not include the use of an additional mechanical pump. These features allowed for a faster synthesis compared to batch procedures with minimal metal leaching.

Introduction

Substituted benzoxazoles have received significant attention from the scientific community due to their occurrence in many active natural and pharmaceutical compounds.[1] In addition, interesting chemical and physical properties of 2-arylbenzoxazoles made these scaffolds also useful for optical applications.[2]

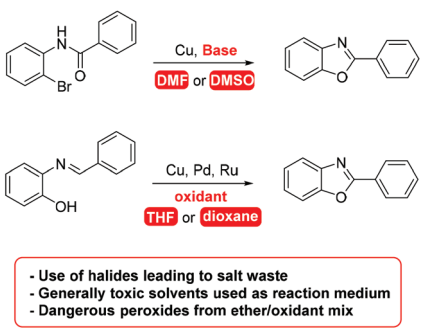
These motivations justify the efforts dedicated to the development of effective procedures to access diversely substituted 2-arylbenzoxazoles. General methods available are based on two main approaches (Scheme 1). The first one is based on the application of metal-catalysis to the intra-molecular *ortho* arylation of *o*-haloanilides or to the domino annulations of *o*-arylhalides with acyl-amides.[3] The second approach consists in the condensation of 2-aminophenol with either a carboxylic acid derivative under acidic/high temperature conditions, or an aldehyde followed by an oxidative cyclization of the preformed phenolic imine.[4]

These synthetic procedures are usually promoted by homogeneous metal catalysts such as Pd, Cu, or Ru.[5] However, very recently the use of heterogeneous metal catalysts has also been explored.[6] Main limitations of these procedures consist in the use of toxic reaction media,[7] and that in the presence of oxidizing reagents, especially when ethers are used as media,[8] dangerous peroxides are generated with evident related safety issues.

Telescoped reaction sequences are commonly adopted to direct the reactivity of intermediates by the consecutive addition of reagents or catalysts to a reactor while avoiding undesired side-processes. As demonstrated by a number of significant examples,[9] these procedures particularly benefit from flow technologies which enable an effective control of the reaction parameters and a proper feeding of the desired reagents in order to steer the reactivity towards the desired pathway.

In addition, flow conditions offer unique advantages in controlling the formation of highly reactive and dangerous intermediates or reagents, improving the safety associated with a synthetic sequence. In this respect, it has also been shown that flow reactors can offer a valid alternative to batch procedures, especially when oxygen is used as a terminal oxidant in a single or multistep synthetic protocol.[10]

In our research program, we are aiming at the definition of chemically and environmentally efficient flow methodologies to access added value materials with a minimal waste pro-



Scheme 1 Common approaches to 2-arylbenzoxazoles.

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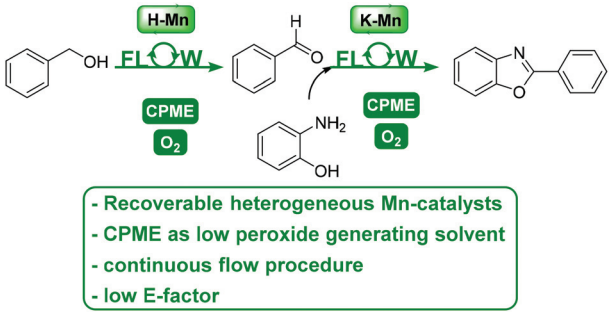


Scheme 2 Features of the present work.

duction.[11] We have recently achieved effective results by combining the use of biomass-derived reaction media, heterogeneous catalytic systems, and flow chemistry technologies in the preparation of target materials including functionalized heterocyclic systems.[12] Under our conditions, we have proved not only that waste can be significantly reduced but also that the flow approach is effective at preserving the catalyst stability and durability while allowing minimal metal leaching and safer handling of highly reactive intermediates.

In this contribution, we report our results on the definition of a multistep continuous flow protocol for the green synthesis of substituted 2-arylbenzoxazoles promoted by heterogeneous mixed valence manganese octahedral molecular sieves (OMSs)[13] using oxygen as an environmentally benign terminal oxidant and cyclopentyl methyl ether (CPME) as a peroxide-safe reaction medium (Scheme 2).

OMSs are constituted of manganese oxide tunnels with a cryptomelane-type morphology. Recently, it has been demonstrated that such materials can catalyse, among other reactions, the oxidative cyclization for the synthesis of aza-containing heterocycles.[14] In this study, we have selected CPME as the solvent, due to its low tendency to generate peroxides compared to a classical ethereal solvent. Moreover, CPME possesses a high stability under acidic or basic conditions, a relatively high boiling point and a low toxicity.[15] For these reasons, CPME has been identified as a promising eco-friendly reaction medium. Additionally, albeit being currently produced by petrochemical means involving cyclopentene and methanol, with its remarkable atom-economical nature,[16] its biogenic production can be envisaged from substrates like cyclopentanol or cyclopentanone,[17] which can be derived from furfural or (bio-based) adipic acid, respectively. As a matter of fact, a recent life-cycle-assessment (LCA) study has shown that the biogenic route leads to a minimized impact, compared to the classic petrochemical approach.[18]

Results and discussion

We began our study by synthesizing two different types of OMSs, following literature procedures (see the ESI†).[13a] We have prepared a potassium-containing OMS (K-OMS) and, after ion exchange using nitric acid, we have obtained an acidic OMS (H-OMS). By microwave plasma atomic emission spectroscopy (MP-AES) analyses, we have measured a manganese loading of 62% in K-OMS and 62% in H-OMS. Additionally, X-ray powder diffraction (XRD) analyses were conducted in order to confirm the expected structure of the catalyst.

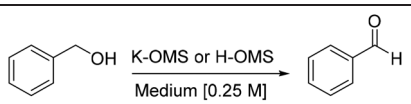
Subsequently, we have studied the oxidation of benzyl alcohol (**1a**) to benzaldehyde (**2a**) as a model reaction for the first step and therefore tested various conditions in batch to simulate the final continuous flow protocol.

First of all, the influence of various reaction media was screened using both H-OMS and K-OMS systems (Table 1).

We noted that H-OMS is generally more efficient compared to K-OMS, while the influence of the different solvents is almost the same on both catalysts. We have screened the reaction media at their reflux temperature to avoid at this stage the additional pressure control. As expected, protic media gave only a poor conversion while ethers and toluene led to excellent results. Among the systems tested, CPME has been selected as the most efficient and environmentally friendly medium for further optimization. Moreover, CPME allowed a minimal leaching of metal among all the tested reaction media, therefore resulting in an expected increased durability of the catalytic systems (see the ESI†).

We also compared H-OMS and K-OMS to other benchmark oxidative conditions (Table 2). Different Mn-based systems were tested to have additional information on the specific structure and properties of OMS catalysts in terms of reactivity and selectivity. Molecular oxygen (Table 2, entries 10 and 11) and hydrogen peroxide (Table 2, entries 12 and 13) were also tested under the same conditions. As expected, the reaction in the presence of potassium permanganate and manganese oxide (Table 2, entries 1–4) gave a good conversion at 24 h, while the selectivity to benzaldehyde **2a** was not satisfactory.

Table 1 Screening of reaction media for the oxidation of **1a** [a]

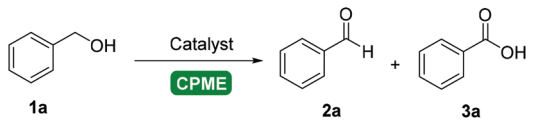


1a **2a**

Entry	Medium	T (°C)	C^b (%) H-OMS	C^b (%) K-OMS
1	Toluene	110	>99	90
2	CH_3CN	82	47	40
3	Toluene/EtOH (1 : 1)	110	29	23
4	Toluene/EtOH (3 : 7)	110	9	9
5	EtOH	78	3	Traces
6	EtOAc	77	38	25
7	BuOH	82	30	30
8	^{t}BuOH	82	41	32
9	Solvent-free	—	2	—
10	2-MeTHF	80	55	52
11	TAME	86	>99	75
12	CPME	106	>99	78

[a] Reaction conditions: **1a** (1 mmol), medium 4 mL [0.25 M], reaction time 30 min, K- or H-OMS: 1 eq. [b] Conversion of **1a**, measured by GLC analyses using samples of pure compounds as reference.

Table 2 Screening of different conditions for the oxidation of **1a** [a]



Entry	Catalyst	Time	C^b (%)	2a/3a
1	$KMnO_4$ (1 eq.)[c]	30 min	20	72/28
2	$KMnO_4$ (20 mol%)	24 h	>99	43/57
3	MnO_2 (1 eq.)[c]	30 min	17	68/32
4	MnO_2 (20 mol%)	24 h	98	89/11
5	K-OMS (20 mol%)	24 h	76	100/0
6	H-OMS (2 mol%)	24 h	26	100/0
7	H-OMS (5 mol%)	24 h	47	100/0
8	H-OMS (10 mol%)	24 h	59	100/0
9	H-OMS (20 mol%)	24 h	>99	100/0
10	O_2 (3 atm)	30 min	—	—
11	O_2 (1 atm)	24 h	3	100/0
12	H_2O_2 (1 eq.)[c]	30 min	—	—
13	H_2O_2 (20 mol%)	24 h	12	92/8

[a] Reaction conditions: **1a** (1 mmol), CPME 4 mL [0.25 M], reaction time 30 min at 106 °C. [b] Conversion of **1a**, measured by GLC analyses using samples of pure compounds as reference. [c] These results can be directly compared to those reported in Table 1, entry 12.

In contrast, the reaction without the catalyst, using molecular oxygen and hydrogen peroxide, gave almost no conversion. These data also suggest that the OMS catalyst and its molecular structure play a specific role in terms of reactivity and selectivity of the system.

With the optimized conditions in hand, we also tested the reusability and durability of our catalytic system H-OMS in the oxidation of benzyl alcohol **1a**. To this end, we screened different approaches to achieve the complete regeneration of the catalyst over consecutive runs (see the ESI†). The most effective procedure for the regeneration of H-OMS was found when the catalyst was washed with either CPME or acetone followed by flushing it with at least 2 bar of oxygen at 100 °C.

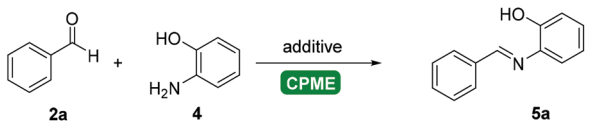
Then, we moved to the optimization of the second and third steps, which involve the formation of imine **5a**, followed by oxidative cyclization to give 2-phenylbenzoxazole **6a**.

First, we investigated the conditions for the preparation of **5a**, which is obviously a process influenced by water. With the initial idea of performing a multistep flow protocol, we kept CPME as the reaction medium and tested whether changes in temperature or the use of additional molecular sieves would facilitate the formation of **5a** by absorbing the water formed during the process. Moreover, we also verified whether the influence of oxygen atmosphere might affect the progress of the imine formation.

After some control experiments in batch, we found that by adding 5 Å molecular sieves to the reaction mixture at reflux temperature the conversion slightly decreased (Table 3, entry 1), while at 120 °C the conversion was almost quantitative.

By considering that the addition of 5 Å molecular sieves did not affect significantly the reaction output leading to some clear benefits, we decided to avoid their use in our further optimization of the flow conditions. In addition, it was noticed that the use of oxygen did not significantly influence the course of the reaction (Table 3, entries 5 and 6).

Table 3 Imine formation from **2a** and **4** [a]



Entry	Additive	T (°C)	C^b (%) to **5a**
1	5 Å MS	106	93
2	5 Å MS	120	>99
3	—	106	>99
4	—	120	>99
5	O_2 (1 atm)	106	96
6	O_2 (1 atm)	120	>99

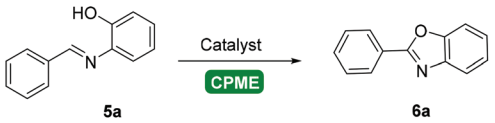
[a] Reaction conditions: **2a** (0.4 mmol), **4** (0.2 mmol), CPME 2 mL [0.1 M], reaction time 10 min. [b] Conversion to **5a**, measured by GLC analyses using samples of pure compounds as reference.

We then moved to the optimization of the third step consisting in the oxidative C–H functionalization/cyclization of the preformed imine **5a** to the finally desired benzoxazole **6a**.

We evaluated the two manganese OMS species in our hand, K-OMS and H-OMS, either in catalytic or stoichiometric amounts, still using CPME as the reaction medium (Table 4).

We found that K-OMS was more efficient than H-OMS in terms of reactivity/reaction time, so we decided to use this catalyst for this last step. It is noteworthy that the reaction gave almost no conversion to **6a** in the absence of any additives or catalysts (Table 4, entries 1 and 2), confirming the role of the catalyst also in this step.

Table 4 Catalyst screening for the formation of 2-phenylbenzoxazole **6a** from oxidative cyclization of **5a** [a]



Entry	Catalyst	Time	C^b (%)
1	—	30 min	—
2	—	24 h	4
3	$KMnO_4$[c]	24 h	7
4	MnO_2[c]	24 h	9
5	K-OMS[d]	30 min	76
6	K-OMS[d]	60 min	>99
7	K-OMS[c]	24 h	>99
8	H-OMS[d]	30 min	54
9	H-OMS[d]	60 min	84
10	H-OMS[c]	24 h	92

[a] Reaction conditions: **5** (1 mmol), CPME 4 mL [0.25 M], 106 °C. [b] Conversion to **6**, measured by GC analyses using samples of pure compounds as reference. [c] 20 mol% of catalyst was used. [d] 100 mol% of catalyst was used.

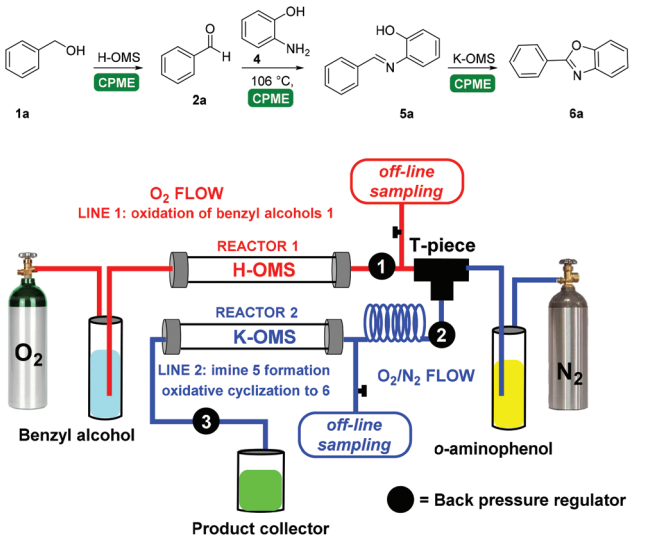
Further, we also tested the reusability of the K-OMS system over consecutive reaction runs. With optimized conditions in hand, we were able to recycle the catalytic system following the same procedure used for the first step in the case of H-OMS for the preparation of **2a**. Then, in order to better predict the durability of the catalyst we also measured the metal leaching during the reaction. To this end, we ran the whole three step synthetic procedure, and after the first reaction, in which the benzaldehyde **2a** was formed from benzyl alcohol **1a**, H-OMS was filtered and 2-aminophenol (**4**) was added. After 10 min of stirring, in order to allow the formation of imine intermediate **5a**, K-OMS was added to promote the formation of 2-arylbenzoxazole **6a**.

Finally, by taking an aliquot of the CPME solution we measured the manganese leaching by MP-AES analyses (see Table 5). Low concentrations of leached manganese were found in solution, suggesting a very good stability of the two catalysts in the applied reaction conditions. We were able to efficiently repeat these measurements over five consecutives reaction runs.

It is worth noting that final product **6a** could be isolated after each run in high purity by simple evaporation of CPME.

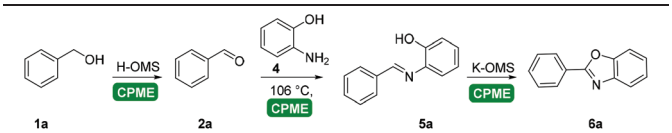
With each of the steps separately optimized, we then focused our attention on the definition of a multistep flow protocol. To this end, we began with the design and assembly of our flow reactor system. Based on the experience gained from our previous studies,[19] we have been proposing a strategy to avoid the use of external pumping systems and the issues related to multi-pumping systems when multistep procedures need to be set. These configurations involve the direct use of a gas to create a flow of the reaction mixture through the reactors containing the catalytic systems. Additionally, in this case we planned to set conditions that would allow the use of an oxygen atmosphere in order to perform in flow the direct regeneration of the catalyst, thus opening to a non-stop continuous flow procedure.

In our case, due to the use of heterogeneous catalytic systems, we packed the two different reactors with the corresponding catalysts, H-OMS and K-OMS, respectively. The system design is shown in Scheme 3, and constituted of two lines containing three main elements: (i) the benzyl alcohols **1** oxidation line; (ii) the loop in which formation of the corresponding imines **5** takes place; and (iii) the oxidative cyclization line. Residence time and flow rate can be controlled by setting the appropriate back pressure regulators (BPRs).



Scheme 3 Multistep flow protocol for the synthesis of benzoxazole **6**.

Table 5 Multistep batch process for the synthesis of **6a** [a]



Run	Yield of **6a** [b] (%)	Mn leaching[c] (ppm)
1	94	7
2	94	3
3	94	3
4	94	3
5	94	2

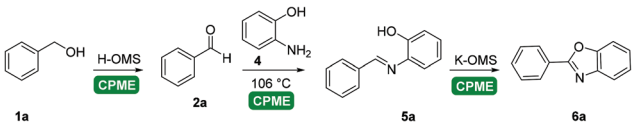
[a] Reaction conditions: **1** (0.4 mmol), **4** (0.2 mmol), CPME 2 mL [0.1 M], temperature was set at 106 °C. [b] Isolated yield of **6a**. [c] Measured by MP-AES analysis.

Initially, O_2 and N_2 were fed at equal flow rates while different back pressures were tested. Using 5 bar pressure of each gas and setting the BPRs for the three sections of the flow apparatus at 2.7, 0.3, and 0.3 bar, respectively (Table 6, entry 1), a poor conversion was achieved due to the short residence time. Setting higher values BPRs, 2-arylbenzoxazole **6a** was formed in 98% yield after an overall 58 min of residence time. It is noteworthy that it is the residence time in reactor 2 that is most crucial for the overall efficiency of the process.

Further optimization directly made in flow concerns the stoichiometry of the reaction (Table 6, entries 5 and 7). To reduce waste generation, we aimed at the formation of the minimal possible excess of aldehyde and found that the generation of 1.2 equivalents of aldehyde **2** with respect to the aminophenol **4** was optimal for the efficiency of the overall process.

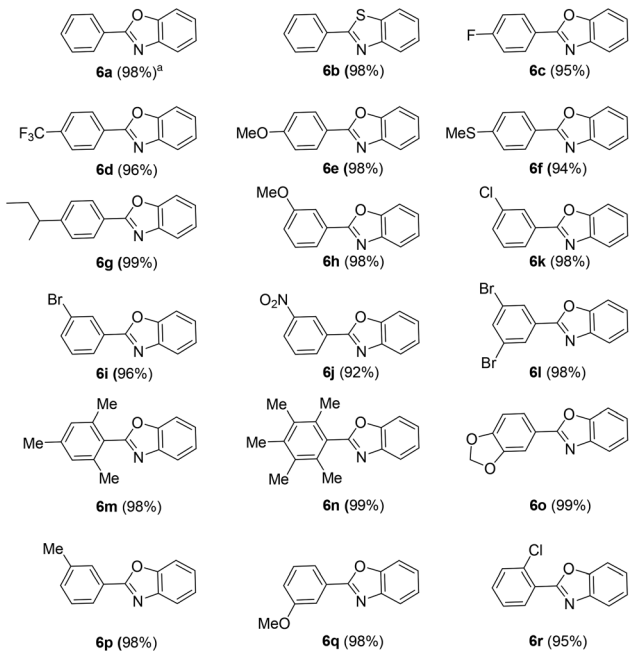
The applicability of our flow protocol was then tested using diversely substituted benzyl alcohols **1** and substituted 2-aminophenol **4** (Scheme 4). With our flow system, we have been able to synthesize a wide range of substituted 2-arylbenzoxazoles **6** in good to excellent yields without isolating any intermediates (aldehydes **2** or imines **5**). Our optimized flow reactor showed an excellent tolerability to halogenated substrates, without leading to dehalogenation side-reactions (Scheme 4, **6c**, **6k**, **6i**, and **6l**). Both electron-rich and electron-poor 2-arylbenzoxazoles **6** were synthesized in high yields. Remarkably, highly substituted substrates and those possessing branched alkyl groups (Scheme 4, **6g** and **6n**) gave very high isolated yields. The flow protocol was also applied to sulphur containing substrates, giving products in excellent

Table 6 Optimization of parameters in the multistep synthesis of **6a** [a]

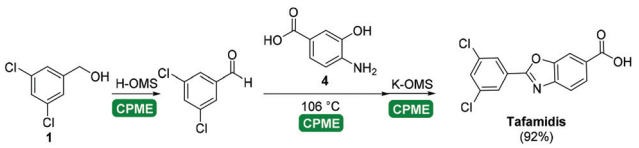


Entry	O_2–N_2 (bar)	BPR 1 (bar)	Flow rate (residence time) In reactor 1	BPR 2 (bar)	BPR 3 (bar)	Loop residence time	Flow rate (residence time) In reactor 2	Yield of **6a** [b] (%)
1	3–3	2.7	0.6 mL min^{-1} (5 min)	0.3	0.3	2 min	0.5 mL min^{-1} (5 min)	23
2	5–5	5.1	0.2 mL min^{-1} (10 min)	2.7	1.4	3 min	0.4 mL min^{-1} (15 min)	44
3	6–6	6.8	0.1 mL min^{-1} (35 min)	2.7	2.7	3 min	0.5 mL min^{-1} (25 min)	64
4	6–6	6.8	0.1 mL min^{-1} (35 min)	5.1	1.4	3 min	0.4 mL min^{-1} (30 min)	84
5	6–6	6.8	0.1 mL min^{-1} (35 min)	5.1	2.7	5 min	0.2 mL min^{-1} (40 min)	87
6	5–5	5.1	0.2 mL min^{-1} (13 min)	5.1	2.7	5 min	0.2 mL min^{-1} (40 min)	96[c]
7	**5–5**	**5.1**	**0.2 mL min^{-1} (13 min)**	**5.1**	**2.7**	**5 min**	**0.2 mL min^{-1} (40 min)**	**98**[c,d]

[a] Reaction conditions: **1** (0.4 mmol) in CPME 2 mL [0.2 M], **4** (0.2 mmol) in CPME 1 mL [0.2 M], temperature was set at 106 °C, column 1 was filled with 78 mg of H-OMS (62% Mn loading, 0.9 mmol of Mn), and column 2 was filled with 68 mg of K-OMS (62% Mn loading, 0.8 mmol of Mn). [b] Isolated yield of **6a**. [c] 1 M solution of **1** and 0.9 M of **4** were used. [d] **1** (0.4 mmol) and **4** (0.37 mmol).



Scheme 4 Substrate scope for the multistep synthesis of benzoxazoles. Isolated yields in parentheses; reaction conditions: **1** (4 mmol) in CPME 4 mL [1 M], **4** (3.3 mmol) in CPME 1.6 mL [2 M], temperature was set at 106 °C, column 1 was filled with 40 mg of H-OMS (62% Mn loading, 0.5 mmol of Mn), and column 2 was filled with 34 mg of K-OMS (62% Mn loading, 0.4 mmol of Mn). [a] **1** (16.0 mmol) in 16 mL of CPME [1 M], **4** (13.4 mmol) in 6.7 mL of CPME.



Scheme 5 Continuous flow synthesis of tafamidis API. Isolated yields in parentheses; reaction conditions: **1** (4 mmol) in CPME 4 mL [1 M], **4** (3.3 mmol) in CPME 1.6 mL [2 M], temperature was set at 106 °C, column 1 was filled with 40 mg of H-OMS (62% Mn loading, 0.5 mmol of Mn), and column 2 was filled with 34 mg of K-OMS (62% Mn loading, 0.4 mmol of Mn).

yields, and especially without detection of disulfides, sulfoxides or sulfones and most importantly without observing any deactivation of the catalyst (Scheme 4, **6b** and **6f**).

With our approach and flow system, we have also been able to define a fast and efficient synthesis of the API tafamidis in 92% yield with an associated *E*-factor value of 4.4 (Scheme 5). Finally, in order to define and quantify a truly waste minimized protocol for the synthesis of 2-arylbenzoxazoles **6a–r**, we have also optimized the recovery of CPME by distilling the solvent from the reaction mixture coming out of the flow reactor. At a reduced pressure (40 mbar) and 50 °C temperature, using a simple distillation apparatus, CPME was recovered almost quantitatively (*ca.* 98%). Its purity was confirmed by ^{1}H- and ^{13}C-NMR analyses, and the recovered solvent was re-used in subsequent runs without further purification.

It is worth noting that by applying our flow protocol we have been able to convert up to 40 mmol with the same catalyst reactors and using almost the same CPME once recycled. Periodic leaching measurements of manganese species were performed during the multi-gram scale flow protocol to check whether the system released metal particles. These analyses showed a very low concentration of Mn (*ca.* 0.17 ppm) in solution (see the ESI†), which corresponds to an overall loss of 0.002% of metal from both H-OMS and K-OMS catalysts. This very low leaching also allowed us to isolate the target compounds **6** in high purity, without need to remove metal contaminants.

Catalytic efficiency is also better preserved in flow conditions; in fact, while regeneration of both catalysts H- and K-OMS in batch requires *ca.* 1 h using 2 bar of oxygen (see comment above) under our flow conditions, this process is immediate, allowing the continuous protocol and the unchanged efficiency of the catalysts over time.

The isolation of the pure product was conducted on the residue coming from the distillation of CPME, by simply washing with a small quantity of ethanol (see the ESI†). It is noteworthy that the entire substrate scope was performed using the same reactors packed with H-OMS and K-OMS (see the ESI†) and also with almost the same CPME recovered by distillation.

Besides the investigation on the substrate scope, we also tested the durability and the stability of our flow system prolonging its use for longer time and larger-scale production of benzoxazole **6a**. To this end, we have let the flow apparatus to operate continuously for 24 h leading 280 mmol of reagents to be converted into the corresponding benzoxazole **6a**, and achieving a productivity of 2.3 g h^{-1} after reaching a steady state (58 min).

To quantify the advantages in terms of waste minimization achieved with our protocols, we calculated the *E*-factor values associated with the synthesis of 2-phenylbenzoxazole **6a**.

For most commonly available protocols, an average *E*-factor of *ca.* 300 is obtained (see the ESI†), but without including in the calculation the significant additional waste generated by the column chromatography purification step necessary to isolate the pure products.

Our batch protocol features an *E*-factor value of 42 for the isolation of products **6** in high purity without the additional purification step.

In addition, our continuous flow protocol features an important low *E*-factor value of 1.7 for the multi-gram scale and 6.4 for the smaller scale procedures (see the ESI†). These values correspond to a *ca.* 98% of waste minimization even without including the additional wasteful silica-gel column purification step that is necessary for other protocols.

Our methodology has allowed us to synthesize the desired 2-aryl benzoxazole products **6a–r** in high yields and low *E*-factors. The flow approach has allowed us to minimize the metal leaching of the heterogeneous catalysts by keeping their efficiency and prolonging their durability. These data prove that future larger scale applications are possible with the obvious technical improvements in the use of mass flow controls and/or on-line analysis to optimize the safety efficiency of the system.

These results confirm that the flow approach combined with heterogeneous catalysis can be a very effective strategy for improving the sustainability of a process by minimizing waste production, prolonging the durability of the catalyst, and making the synthetic procedure operationally simpler compared to batch conditions and in general compared to the reported available protocols.[20]

Conclusions

In conclusion, in this contribution we have reported a highly chemically efficient and waste-minimized procedure for the multistep synthesis of 2-arylbenzoxazoles **6a–r** in 92–99% isolated yields in a continuous flow regime. The utility of the protocol is also confirmed by its applicability to a variety of functionalities and its capability to be executed on a multi-gram scale. The use of the heterogeneous manganese-based catalysts (OMS) in combination with CPME as a reaction medium allowed the desired products to be obtained with excellent yields and good hourly productivity. CPME has proved to be the most efficient medium in this oxidative protocol performed under an oxygen flow, and it is also the safest option considering its stability for peroxide formation. The recovery and reuse of the reaction medium and the durability of the catalyst make our protocol also very efficient in terms of waste minimization, as proven by the low associated *E*-factor, and purity of the final product in which minimal leaching of metal species has been found.

Experimental section

Multi-gram scale continuous flow procedures and *E*-factor calculation (280 mmol)

Reservoir 1 was charged with 1 M CPME (300 mL) solution of benzyl alcohol (308 mmol, 33.3 g, 32 mL), then the oxygen line was set to 5 bar of pressure, and the solvent started to flow through column 1 (filled with 78 mg of H-OMS) at a flow rate of 0.2 mL min^{-1} with a residence time of 13 minutes. When the flow reached the exit of column 1, the nitrogen line was set to 5 bar and the *o*-aminophenol solution (280 mmol, 30.5 g in 300 mL of CPME 0.9 M) previously charged into reservoir 2 started to mix with flow 1 into a T-piece. The resulting mixture continuously flowed through the loop, in which imine formation took place, before reaching column 2 (filled with 68 mg of K-OMS) at a flow rate of 0.2 mL min^{-1} with a residence time of 40 min. At the end of the process, the system was completely flushed, both lines with 55 mL of CPME in order to wash the catalyst columns. The product was collected into the product reservoir. Then, CPME was recovered *via* distillation under reduced pressure (98% of the total amount, confirmed by ^{1}H-NMR), and the residue was washed with 90 mL of EtOH in order to remove unreacted benzaldehyde, furnishing pure product **6** (274.4 mmol, 53.5 g) in 98% yield with a productivity of 2.3 g h^{-1} after the steady state was reached.

E-factor = [610 g (CPME) + 33.3 g (benzyl alcohol) + 30.5 g (*o*-aminophenol) + 71 g (EtOH)] − [598 (CPME recovered) + 53.5 g (product, 98% yield)]/[53.5 g (product, 98% yield)] = 1.7.

Conflicts of interest

There are no conflicts of interest to declare.

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