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Sequential Continuous-Flow Synthesis of 3-Aryl Benzofuranones

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Abstract: A sequential continuous-flow system to produce 3-aryl benzofuranones was developed. Starting from 2,4-di-*tert*-butylphenol and glyoxylic acid monohydrate, both the initial cyclocondensation and the subsequent Friedel–Crafts alkylation were catalyzed by the same heterogeneous catalyst, Amberlyst-15H. The catalyst has a promising lifetime for these two steps, and it was able to be recovered and reused for several runs without deactivation. By using the established flow system, 5,7-di-tert-butyl-3-(3,4-dimethylphenyl)-3H-benzofuran-2-one (Irganox HP-136), which is a commercial antioxidant, was prepared in 88% two-step yield. Reactions with various aromatic compounds proceeded well under flow conditions to afford 3-aryl benzofuranone derivatives in high yields with good functional group compatibility.

In recent decades, aryl benzofuranones and related derivatives have attracted wide attention because of their various biological activities, pharmacological applications, and industrial relevance.[1] A typical example is their application as a carbon-centered radical antioxidant in the polymer industry.[2] Indeed, 5,7-di-*tert*-butyl-3-(3,4-dimethylphenyl)-3*H*-benzofuran-2-one (Irganox HP-136) has an excellent ability to donate a benzylic hydrogen atom with concomitant formation of a highly stable benzofuranonyl free radical, which has led to this compound being used as a commercial antioxidant to stabilize hydrocarbon polymers in melt processing at a high temperature.[3]

Several synthetic routes to α-aryl benzofuranones have been developed. A seminal report utilized *p*-TsOH-catalyzed cyclocondensation of glyoxylic acid with phenol starting materials, followed by a Friedel–Crafts alkylation.[4] An alternative approach involves formation of mandelic acids first, followed by $Ni(OTf)_2$-catalyzed tandem Friedel–Crafts/lactonization reaction with phenol derivatives at 160 °C to give the target molecules.[5] A TfOH-catalyzed cascade *ortho* C–H activation/lactonization of phenols with α-aryl-α-diazoacetates was also reported that enabled the synthesis of Irganox HP-136.[6] Other reports[7] also described possible synthetic methods. However, the processes summarized above all employ expensive catalysts, or toxic and explosive reagents, or proceed under harsh reaction conditions, which are not suitable for sustainable industrial productions. A more efficient, environmentally compatible, and easily operated process is highly desired.

The development of a sequential continuous-flow method offers an ideal strategy. In general, flow reactions present numerous advantages over conventional batch reactions with respect to environmental compatibility, reaction efficiency, and operational safety.[8] In particular, heterogeneous reactions using packed column reactors are attractive as the work-up is much simplified as there is no requirement for filtration of catalysts which in batch, can result in catalyst residues or quenching agents which may contaminate the product.[9] This particular characteristic is particularly important for planning sequential multistep flow synthesis. Here, we describe our approach to the synthesis of 3-aryl benzofuranones in two sequential-flow steps, with each step catalyzed by the same heterogeneous acid catalyst, Amberlyst-15H (Scheme 1).

2,4-Di-*tert*-butylphenol (**1**) and glyoxylic acid monohydrate[10] were selected as starting materials for the optimization of reaction conditions. Initially, the reactions were performed in dichloroethane (DCE) under reflux conditions, and several heterogeneous acid catalysts were screened, as shown in Table 1. All the selected catalysts, including both Lewis and Brønsted acids, gave moderate to good yields (entries 1–6). In entries 4 and 6, decomposition of the starting material was observed to give low yields. In other cases, the reactions were incomplete and most of the starting materials remained. Among them, Amberlyst-15H showed the best performance; this material is a sulfonic acid bearing cation-exchange resin that is widely used in organic synthesis because of its environmental benefits and excellent reusability.[10] Amberlyst-15H can be used to promote the formation of benzofuran effectively, avoiding the use of metals with all the associated drawbacks such as toxicity, higher cost, and the eventual necessity of complex ligands and threshold values in pharmaceutical products. When considering the feasibility of a flow operation, the solubility of the starting materials in the reaction system is crucial. Given the poor solubility of glyoxylic acid in dichloroethane (DCE) and PhCl (entries 1 and 7), further screening was required to find an appropriate solvent. Reactions in DMF, MeCN, and THF did not proceed, and only phenol **1** remained. Alcohol solvents dissolve glyoxylic acid very well, and, promisingly, the reaction in trifluoroethanol gave the product in 93% yield in the presence of Amberlyst-15H at 80 °C after stirring for 3 h(entry 13).

With the selected catalyst and solvent in hand, a flow system for the cyclocondensation step was set up. After the initial tuning of reaction parameters such as temperature, flow

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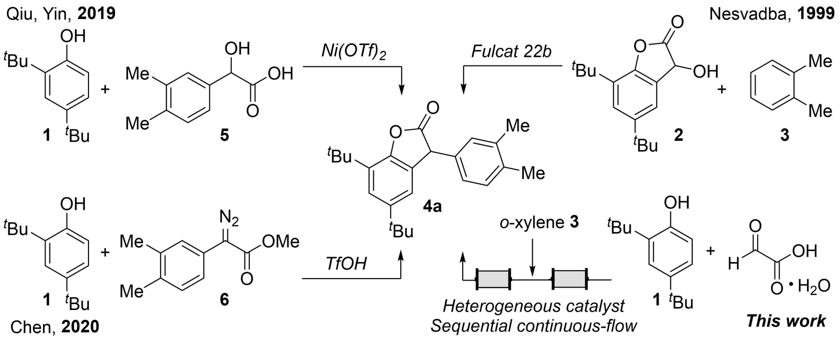
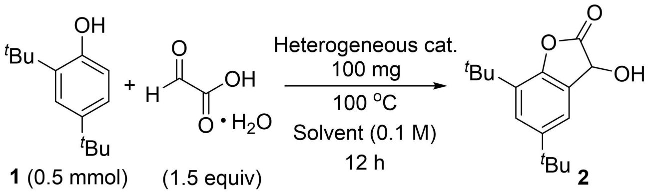


Scheme 1. Reported synthetic routes to Irganox HP-136 and this work.

Table 1. Screening of heterogeneous acid catalysts and solvents for the cyclocondensation step.



Entry	Catalyst	Solvent	Yield [%][a]
1	Amberlyst 15H	DCE	90
2	Zr-Zeolite	DCE	44
3	MC-Sc(OTf)$_3$	DCE	81
4	Nafion	DCE	65
5	Dowex H$^+$	DCE	10
6	Si-Tosic acid	DCE	40
7	Amberlyst 15H	PhCl	95
8	Amberlyst 15H	DMF	trace
9[b]	Amberlyst 15H	MeCN	trace
10[b]	Amberlyst 15H	THF	trace
11[b]	Amberlyst 15H	EtOH	40
12[b]	Amberlyst 15H	CF_3CH_2OH	93
13[b,c]	Amberlyst 15H	CF_3CH_2OH	93

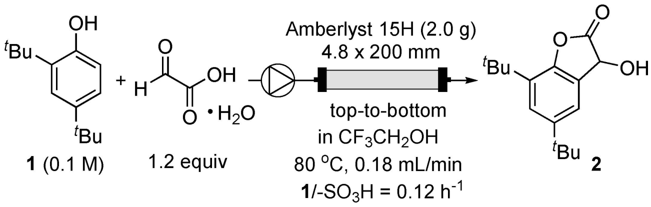
[a] Determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as internal standard. [b] Reaction temperature was 80 °C. [c] Reaction time was 3 h.

rate, catalyst loading, and flow direction, the basic flow setup was established as shown in Figure S1 (see Supporting Information (SI)). A stock solution of 0.1 M 2,4-di-*tert*-butylphenol (**1**) and glyoxylic acid monohydrate (1.2 equiv) in trifluoroethanol was flowed using a pump at a flow rate of 0.18 mL/min through an SUS column (4.8 mm × 200 mm) packed with 2.0 g of Amberlyst-15H (total acid amount; 8.8 meq, the ratio of **1** fed per an hour to sulfonic acid sites, **1**/-SO_3H was calculated to be 0.12 h^{-1}.). A column heater was employed to heat the flow column reactor at 80 °C, the column reactor was set vertically, and the flow direction was fixed as top-to-bottom, which gave an improved and more stable reaction performance. We estimated the void volume of the 4.8 × 200 mm SUS column (3.6 mL) was 2.8 mL, thus an ideal residence time of the reaction at 0.18 mL/min substrates flow was calculated to be 15.6 min. The outlet of the flow reactor was connected to a reservoir and the product sample solution was collected for 2 h during 120 h operation. Under the standard flow conditions shown in Table 2, the desired product **2** was constantly obtained in 91–94% yields. No deactivation was observed after continuous reaction for 120 h. The overall reaction economy was assessed by evaluating the process mass intensity (PMI),[11] which confirmed the advantages of using heterogeneous catalysts; the trifluoroethanol solvent could also be reused in the flow system (Table 2). Indeed, recycling experiments, carried out using recovered trifluoroethanol and reusing the catalyst-packed reactor with the same contents, confirmed that consistently high yields were achieved for four runs.

We then focused on developing the second Friedel–Crafts alkylation under flow conditions. Preliminary investigations were conducted under batch conditions using purified 3-hydroxy-benzofuranone **2** (Table 3). Interestingly, Amberlyst-15H was also the best catalyst for this step (entry 1), although the reaction required a higher temperature (entry 6). Various solvents gave good yields (> 95%) at 120 °C. Notably, the reaction in trifluoroethanol resulted in a high yield, suggesting the possibility of using this solvent in a sequential flow system. In addition, the use of *o*-xylene (**3 a**) itself as solvent allowed the reaction temperature to be reduced to 105 °C, and the desired **4 a** was obtained in 95% yield.

We next designed three flow setups for the Friedel–Crafts alkylation under continuous-flow conditions (Table 4). In en-

Table 2. Continuous-flow cyclocondensation reaction.



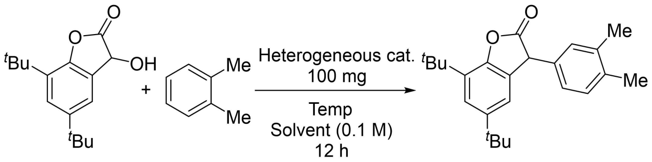
Amberlyst 15H (2.0 g)
4.8 x 200 mm
top-to-bottom
in CF_3CH_2OH
80 °C, 0.18 mL/min
1/-SO_3H = 0.12 h^{-1}

1 (0.1 M) 1.2 equiv **2**

Time [h]	2–4	4–6	6–8	22–24	118–120
Yield [%][a]	91	94	93	91	92
Run[b]	1st		2nd	3rd	4th
Yield [%][a,c]	94		92	93	92

[a] Determined by ^1H NMR analysis using 1,1,2,2-tetrachloroethane as internal standard. [b] CF_3CH_2OH was recovered by distillation and reused for the 2nd, 3rd, and 4th runs; The same column-packed Amberlyst 15H was used for each run. [c] Yield after 16–18 h was determined.

Table 3. Screening of heterogeneous acid catalysts and solvents for the Friedel–Crafts alkylation.



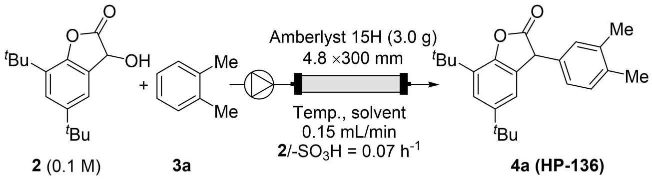
Heterogeneous cat. 100 mg
Temp
Solvent (0.1 M)
12 h

2 (0.5 mmol) **3a** (5.0 equiv) **4a (HP-136)**

Entry	Catalyst	Solvent	Temp. [°C]	Yield[a] [%]
1	Amberlyst 15H	PhCl	100	62
2	Zr-zeolite	PhCl	100	trace
3	MC-Sc(OTf)$_3$	PhCl	100	10
4	Nafion	PhCl	100	40
5	Amberlyst 15H	PhCl	110	75
6	Amberlyst 15H	PhCl	120	95
7	Amberlyst 15H	*o*-xylene	105	95
8	Amberlyst 15H	CF_3CH_2OH	120	97
9	Amberlyst 15H	dichlorobenzene	120	96

[a] Determined by ^1H NMR analysis using 1,1,2,2-tetrachloroethane as internal standard.

Table 4. Continuous-flow Friedel–Crafts alkylation.



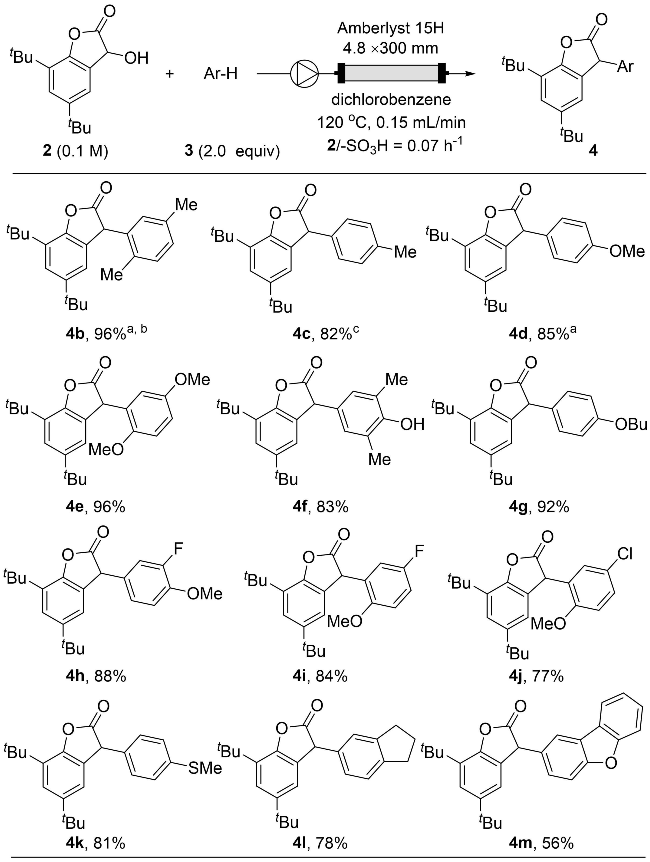
Amberlyst 15H (3.0 g)
4.8 ×300 mm
Temp., solvent
0.15 mL/min
2/-SO_3H = 0.07 h^{-1}

2 (0.1 M) **3a** **4a (HP-136)**

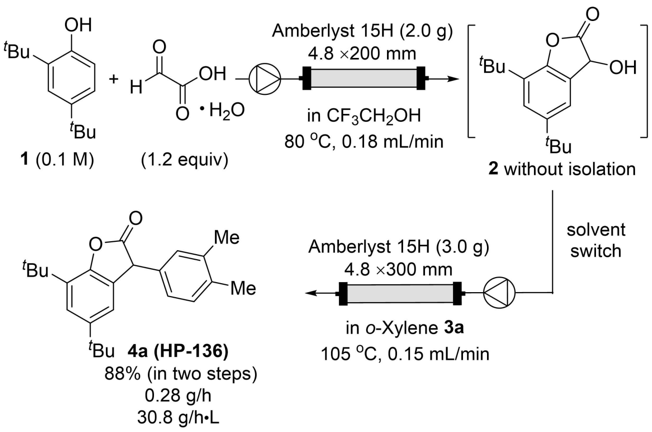
Entry	Solvent	Temp[°C]	Yield[a] [%]		
			4–6 h	6–8 h	98–100 h
1	*o*-xylene	105	92	94	92
2[b]	CF_3CH_2OH	120	41	37	
3[b]	dichlorobenzene	120	92	93	93

[a] Determined by ^1H NMR analysis using 1,1,2,2-tetrachloroethane as internal standard. [b] 5.0 equiv. of **3a** were used.

try 1, a stock solution of **2** (0.1 M, isolated) in *o*-xylene **3a** was prepared. The prepared solution was flowed at a flow rate of 0.15 mL/min through an SUS column (4.8 mm × 300 mm diameter) packed with 3.0 g of Amberlyst-15H (total acid amount; 13.2 meq). In this case, over 92% yield of **4a** was obtained and the yield was kept for over 100 h. Although the batch reaction gave a good yield when it was performed in trifluoroethanol using a sealed tube to allow the reaction to reach the indicated temperature, in the flow system the reaction using trifluoroethanol led to refluxing in the flow column and gave a disappointing yield.[12] It turned out that the use of a higher boiling point solvent would be a better choice for this flow



Scheme 2. Substrate scope for the Friedel–Crafts alkylation in flow. [a] Ar-H as solvent. [b] Temperature was 105 °C. [c] Solvent was a mixture of ArH/dichlorobenzene = 1 : 9.



Scheme 3. Sequential continuous-flow synthesis of **4a** (Irganox HP-136).

reaction. The results shown in entry 3 demonstrated the use of alternative conditions for the flow reaction, with a stock solution of **2** (isolated, 0.1 M) and 5.0 equiv. of *o*-xylene (**3a**) in dichlorobenzene. Similar to the results summarized in entry 1, excellent yields of the product **4a** were obtained.

With the above information in hand, we managed the solvent in this flow system to expand the substrate scope for a series of aromatic substrates to afford the target 3-aryl benzofuranones. The substrate scope for the Friedel–Crafts alkylation is summarized in Scheme 2. The final 10 mL resulting solution for each substrate was concentrated and purified by column chromatography to afford isolated **4** (see SI). For liquid aromatic substrates, such as *p*-xylene (**3b**) and anisole (**3d**), the reactions were conducted under neat conditions with a solvent amount of those aromatics to produce the corresponding products **4b** and **4d** in 96% and 85% yields, respectively. For the synthesis of **4c**, the Ar-H was a commonly used reagent, but the indicated reaction temperature was higher than the boiling point, so a mixed solution of Ar-H/dichlorobenzene (1 : 9) was used. For substrates **3e**–**m**, which are mainly solid aromatics at ambient temperature, 2.0 equiv. of these Ar-H were used as dichlorobenzene solutions, which was sufficient to promote the reaction in moderate to good yields. Phenol, halogen, ether, and thioether moieties were well tolerated. The regioselectivity was directed by both electronic density and steric effects.

Based on the present systematic optimization, a two-step continuous-flow synthesis of Irganox HP-136 was demonstrated (Scheme 3). The cyclocondensation step was conducted under the established flow conditions to yield a solution with high yield of **2**. After a simple solvent switch from trifluoroethanol to *o*-xylene to make a 0.1 M solution, the Friedel–Crafts alkylation was conducted in another flow reactor under the indicated reaction conditions for 6 h. At this stage we conducted solvent exchange as an off-line manner. Finally, a total yield of 88% over the two steps was confirmed by an isolation from 54 mL of the product solution. We also tested a mixed solvent without solvent switching and found that the system could provide a similar two-step yield (see SI). Considering the recycling of the solvent and total TON of this reaction, we envision the above method as the optimal.

In conclusion, we have developed a sequential continuous-flow system to produce 3-aryl benzofuranones through a cyclocondensation and subsequent Friedel–Crafts alkylation. Notably, both the steps were catalyzed by the same heterogeneous catalyst, Amberlyst-15H, under the indicated reaction conditions. 5,7-Di-*tert*-butyl-3-(3,4-dimethylphenyl)-3*H*-benzofuran-2-one (Irganox HP-136), which is a commercial antioxidant used to stabilize hydrocarbon polymers in melt processing at a high temperature, was prepared by using the current flow method in 88% two-step yield. In addition, various aromatics reacted with intermediate **2** to afford 3-aryl benzofuranone derivatives under the flow conditions in high yields with good functional group compatibility.

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Conflict of Interest

The authors declare no conflict of interest.

Keywords: Continuous-flow · Heterogeneous catalyst · Amberlyst-15H · 3-Aryl Benzofuranones · Irganox HP-136

[1] a) H. Ding, P. L. DeRoy, C. Perreault, A. Larivee, A. Siddiqui, C. G. Caldwell, S. Harran, P. G. Harran, *Angew. Chem.* **2015**, *127*, 4900–4904; *Angew. Chem. Int. Ed.* **2015**, *54*, 4818–4822; b) G. Tommonaro, N. Garcia-Font, R. M. Vitale, B. Pejin, C. Iodice, S. Canadas, J. Marco-Contelles, M. Oset-Gasque, *J. Med. Chem.* **2016**, *122*, 326–338; c) K. C. Nicolaou, S. A. Snyder, X. H. Huang, K. B. Simonsen, A. E. Koumbis, A. Bigot, *J. Am. Chem. Soc.* **2004**, *126*, 10162–10173; d) J. Lin, B. S. Gerstenberger, N. Y. T. Stessman, J. P. Konopelski, *Org. Lett.* **2008**, *10*, 3969–3972; e) N. David, R. Pasceri, R. R. A. Kitson, A. Pradal, C. J. Moody, *Chem. Eur. J.* **2016**, *22*, 10867–10876; f) S. Bahri, R. B. Ali, R. Abdennabi, D. B. Said, M. Mlika, M. K. B. Fradj, M. V. E. May, S. B. K. Jameleddine, *Nutr. Cancer.* **2020**, *72*, 283–292; g) Y. Y. Ma, D. G. Zhao, R. Zhang, X. He, B. Q. Li, X. Z. Zhang, Z. Wang, K. Zhang, *Food Funct.* **2020**, *11*, 1692–1701.

[2] P. Nesvadba, S. Evans, C. Kröhnke, J. Zingg, Ger. Offen. 4432732, **1995**.

[3] a) X. Meng, Z. Xin, X.-f. Wang, *Polym. Degrad. Stab.* **2010**, *95*, 2076; b) I. Rex, B. A. Graham, M. R. Thompson, *Polym. Degrad. Stab.* **2005**, *90*, 136.

[4] P. Nesvadba, L. Bugnon, P. Dubs, S. Evans, *Synlett* **1999**, *1999*, 863–864.

[5] Z. Tang, Z. Tong, Z. Xu, C. T. Au, R. Qiu, S. F. Yin, *Green Chem.* **2019**, *21*, 2015–2022.

[6] S. Hu, Z. Lu, M. Liu, H. Xu, J. Wu, F. Chen, *J. Org. Chem.* **2020**, *85*, 23, 14916–14925.

[7] a) M. Gerster, R. Wicki, *Synthesis* **2004**, *2004*, 249–254; b) B. B. Dhotare, M. K. Choudhary, S. K. Nayak, *Synth. Commun.* **2016**, *46*, 1772–1780; c) T. Satoh, T. Tsuda, Y. Terao, M. Miura, M. J. Nomura, *Mol. Catal. Chem.* **1999**, *143*, 203–210; d) X. Qi, H. P. Li, X. F. Wu, *Chem. Asian J.* **2016**, *11*, 2453–2457; e) H. P. Li, H. J. Ai, X. Qi, J. B. Peng, X. F. Wu, *Org. Biomol. Chem.* **2017**, *15*, 1343–1345; f) X. F. Cheng, Y. Li, Y. M. Su, F. Yin, J. Y. Wang, J. Sheng, H. U. Vora, X. S. Wang, J. Q. Yu, *J. Am. Chem. Soc.* **2013**, *135*, 1236–1239; g) M. Yang, X. Jiang, W. J. Shi, Q. L. Zhu, Z. J. Shi, *Org. Lett.* **2013**, *15*, 690–693; h) R. K. Rit, M. R. Yadav, A. K. Sahoo, *Org. Lett.* **2014**, *16*, 968–971; i) M. Santi, D. M. C. Ould, J. Wenz, Y. Soltani, R. L. Melen, T. Wirth, *Angew. Chem. Int. Ed.* **2019**, *58*, 7861–7865; *Angew. Chem.* **2019**, *131*, 7943–7947.

[8] a) S. Kobayashi, *Chem. Asian J.* **2016**, *11*, 425–436; b) T. Tsubogo, H. Oyamada, S. Kobayashi, *Nature* **2015**, *520*, 329–332; c) H. Ishitani, Y. Saito, T. Tsubogo, S. Kobayashi, *Org. Lett.* **2016**, *18*, 1346–1349.

[9] W.-J. Yoo, H. Ishitani, Y. Saito, B. Laroche, S. Kobayashi, *J. Org. Chem.* **2020**, *85*, 5132–5145.

[10] For selection of the starting material, please see the supporting information.

[11] E. R. Monteith, P. Mampuys, L. Summerton, J. H. Clark, B. U. W. Maes, C. R. McElroy, *Green Chem.* **2020**, *22*, 123–135.

[12] Because the reaction temperature was much higher than the boiling point of trifluoroethanol, the refluxing was still observed when using a back pressure regulator, which resulted in some amounts of the product remaining in the column.

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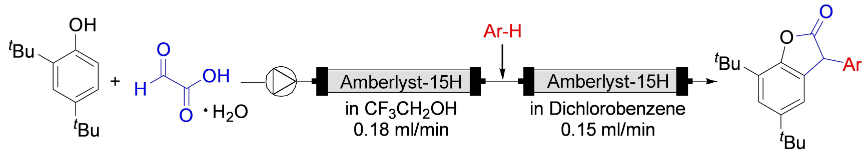

A sequential continuous-flow system to produce 3-aryl benzofuranones via an initial cyclocondensation and subsequent Friedel-Crafts alkylation catalyzed by the same reusable heterogeneous catalyst, Amberlyst-15H, was developed. Various 3-aryl benzofuranone derivatives under flow conditions were synthesized in high yields with good functional group compatibility. A commercial antioxidant Irganox HP-136 was prepared in 88% two-step yield.

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