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Microwave Heated Continuous Flow Palladium(II)-Catalyzed Desulfitative Synthesis of Aryl Ketones

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ABSTRACT

A protocol for Pd(II)-catalyzed desulfitative synthesis of aryl ketones from sodium aryl sulfinates and nitriles in continuous flow has been developed. The reactions proceed with microwave heating using microwave transparent tube reactors, affording the desired aryl ketones in fair to good yields. Microwave transparent aluminium oxide reactors were identified as a safe and thermostable alternative to borosilicate glass reactors.

Keywords: Flow synthesis, Aluminium oxide, Borosilicate glass, Silicon carbide, Microwave, Aryl sulfonate

INTRODUCTION

Dedicated instruments for small-scale batch synthesis employing microwave (MW) heating are now routinely used in chemistry labs, both due to their design that enables safe processing at elevated temperatures and pressures, and because of the speed of MW heating.^{1–5} Thus, MW synthesizers were early combined with flow technology, both using stop-flow and continuousflow (CF) approaches.^{6–14} These systems were often modified commercial MW batch instruments.^{8–12,14} We recently reported on a dedicated system for CF synthesis utilizing nonresonant MW heating and 200 mm long, ϕ_i 2-6 mm, MW transparent borosilicate glass (BSG) tube reactors.^{15,16} Since BSG is a MW transparent material¹⁷ the reaction mixture is heated directly with this type of reactor. In contrast, silicon carbide (SiC) reactors are MW absorbing and heat the reaction mixture in a more conventional manner.¹⁸ Due to their ability to withstand the stress caused by MW induced hot-spots at higher temperature that may form if metal is deposited on the internal surface of the reactor, SiC reactors have been identified as a safe and useful alternative for MW heated metal-catalyzed flow reactions.¹⁹

Aluminum oxide (AlOx) is a complementary MW transparent and highly thermostable ceramic material - properties which make it especially interesting in the case of continuous flow MW assisted organic synthesis (CF-MAOS). Though AlOx is a common material used in standard flow chemistry applications^{20–23}, to our knowledge this material has not previously been evaluated as a reactor material for CF-MAOS.

Our group's interest in Pd-catalyzed reactions has prompted us to develop CF-MAOS protocols for reactions such as the Suzuki-Miyaura reaction^{15,19,24}, the Mizoroki-Heck reaction¹⁹, an oxidative Heck vinylation reaction¹⁵, and a decarboxylative Pd(II)-catalyzed 1,2-addition reaction producing amidines²⁵.

In parallel, we have with great interest followed and participated in the development of sodium arylsulfinates as aryl-Pd precursors. These substrates have recently emerged as useful alternatives to benzoic acids as arylating agents in Pd(II)-catalyzed cross-couplings since they are not limited to electron-rich, sterically congested, *ortho*-substituted moieties.^{25–27} The first synthesis of aryl ketones from aryl sulfinates by Pd(II)-catalyzed 1,2-addition to nitriles were independently reported by Wang²⁸, Deng²⁹ and ourselves^{30,31}, and has since then been followed by other oxidative applications such as biaryl synthesis^{32–37}, Heck-type reactions^{38–41}, conjugate addition reactions^{42,43}, hydroarylations⁴⁴, arylations through C-H activation^{45–47} and ring opening addition to oxabicyclic alkenes⁴⁸.

In this report we further investigate desulfitative reactions by developing a CF-MAOS protocol for the Pd(II)-catalyzed synthesis of aryl ketones from sodium aryl sulfinates and nitriles.

RESULTS AND DISCUSSION

Based on our previous work in batch,^{30,31} we envisioned an adapted protocol for a continuous flow MW assisted organic synthesis (CF-MAOS) of aryl ketones using the instrument setup presented in Figure 1. The selected model reaction between sodium 4-methylbenzenesulfinate (1a) and benzyl cyanide (2a) depicted in Table 1 constitutes a challenging system for use in CF-MAOS as the use of hydrophobic nitriles such as benzyl cyanide results in a biphasic reaction mixture. After initial attempts we decided to use a simplified reaction setup with one stock solution rather than separating the reaction components as we found that vigorous stirring produced an emulsion which could be pumped into the reactor in a controlled fashion (see Figure

2).



Figure 1. a) Setup for CF-MAOS showing pump (left), generator with MW applicator on top (middle) and fraction collector (right). b) Close-up of MW applicator with the front piece unmounted and a borosilicate glass (BSG) tube reactor inside the helical antenna.



Figure 2. a) Biphasic reaction mixture without stirring. b) Reaction mixture with vigorous stirring. c) Reaction mixture in reactor with applied MW heating.

Thus, a stock solution with 75 mM **1a** (1.0 equiv), Pd(O₂CCF₃)₂ (8%), 6-methyl-2,2'-bipyridyl (12%), **2a** (5.0 equiv) and TFA (10 equiv) in H₂O/THF (1:1) was pumped through a 200 mm, θ_i 3 mm, BSG tube reactor with an applied axial MW field covering 120 mm of the reactor to determine suitable reaction temperature and time. The use of MW radiation provides fast heating and allows for rapid screening of reaction temperatures. However, conventional methods like thermocouples and mercury thermometers for measuring the temperature of the reaction mixture are affected by the electromagnetic field in the reactor.^{49–51} Consequently, the available options for accurate monitoring the reaction temperature are limited and made us opt for an Optris CSmicro 3M IR sensor which has previously been shown to provide an accurate estimation of the temperature of the reaction mixture (correlated to measurements by a fiber-optic sensor).⁵² This sensor has a spectral response that allows measurement of reaction temperatures through BSG. For the outcome of the optimization work, see Table 1.

Table 1. Optimization of Reaction Temperature for CF-MAOS Using a Borosilicate Glass **(BSG)** Tube Reactor



The borosilicate glass (BSG) reactor was 200 mm long ϕ_i 3 mm and the axial MW field covered 120 mm of the reactor.^a The temperature was measured using an Optris CSmicro 3M IR sensor. ^b Calculated as the time the reaction mixture stays in the irradiated zone of the reactor, corresponding to the width of the MW field. ^c Isolated yield. >95% purity according to ¹H NMR. ^c Determined by GC-MS.

When pumped through the system the emulsion quickly separated into a segmented flow but the reaction seems to occur even though mixing between the phases is limited at the beginning of the tube reactor (Figure 2). The best yield of **3aa** was obtained at 120 °C and at a flow rate of 1 mL/min, corresponding to 50 s in the MW field (Table 1, Entry 4). A lower flow rate of 0.5 mL/min and thus a longer residence time of the reaction mixture in the heated zone of the reactor gave a lower yield (Entry 3). The reaction temperature also proved more difficult to control at 0.5 mL/min, probably due to the different MW absorbing characteristics of the heterogenous system, which had more impact at a lower flow rate. Increasing the flow rate to 2 mL/min

resulted in somewhat reduced yield (Entry 5). The conditions presented in Entry 4, Table 1, were thus chosen for investigation of the scope of the protocol, providing a good balance between process control, production rate and product yield. With these parameters the processing time was 8 minutes for a reaction at 0.6 mmol scale and the aryl ketone **3aa** could be produced at a rate of 4.3 mmol/h.



Figure 3. a) Tube reactors of different materials employed for the Pd(II)-catalyzed desulfitative addition of sodium aryl sulfinates to nitriles. Silicon carbide, SiC, (left), borosilicate glass, BSG, (middle), and aluminum oxide, AlOx (right). All the reactors are of 200 mm length and øi 3 mm. b) Temperature profiles for heating benzene at 1 mL/min flow rate using different reactor materials. The temperature was measured using an Optris CSmicro 3M IR sensor for the BSG reactor, and an Optris CT IR sensor with a LT22 sensing head for the AlOx and SiC reactors.

Next, we decided to investigate the use of other reactor materials (see Figure 3a). Like BSG, AlOx is a MW transparent material while SiC absorbs MWs. AlOx reactors may serve as a safer alternative to BSG reactors as they are more thermostable (maximum operating temperature 1950 °C compared to 500 °C, see Supporting Information). The behavior of these reactor

materials under MW irradiation is illustrated by the heating profiles in Figure 3b. The temperature for the BSG tube reactor is measured using a sensor designed for measurement of the temperature of the solvent (Optris CSmicro 3M), while for the AIOx and SiC reactors a different sensor which measures the outside temperature of the reactor is used (Optris CT with a LT22 sensing head). The measured temperature increases slowly for MW transparent reactors (BSG and AIOx) as benzene absorbs very little of the MW radiation due to the low dissipation factor (tan $\delta = 1.4 \times 10^{-3})^{53}$, while the SiC reactor is quickly heated by absorbing the MWs. AIOX (tan $\delta = 3.8 \times 10^{-4}$) is more MW transparent than BSG (tan $\delta = 37 \times 10^{-4}$) which may contribute to a slower heating rate of benzene. Further, the measured temperature for the AIOx reactor probably also increases more slowly compared to the BSG reactor due to the fact that the outside temperature of the reactor is measured and not the reaction mixture which is heated directly by the MWs. Despite the heterogeneous reaction mixture, the temperature read-out was stable under MW processing for all three reactor materials.

The reaction between **1a** and **2a** was chosen as the model reaction for the study of the different reactor materials. The reactions were performed at different temperatures (100 °C, 120 °C and 140 °C) and the isolated yields of the most productive conditions (as determined by GC-MS) are shown in Table 2.

Table 2. Pd(II)-Catalyzed Desulfitative Addition Reactions of Sodium Aryl Sulfinates to Nitriles using Tube Reactors of Different Materials



The reactors were 200 mm long ϕ_i 3 mm and the axial MW field covered 120 mm of the reactor. ^a The temperature was measured using an Optris CSmicro 3M IR sensor for the BSG reactor, and an Optris CT IR sensor with a LT22 sensing head for the AlOx and SiC reactors. ^b The heated zone corresponds to: the width of the MW field for the BSG and AlOx reactors, or to the full length of the reactor for the SiC reactor. ^c Calculated as the time the reaction mixture stays in the heated zone of the reactor. ^d Isolated yield. >95% purity according to ¹H NMR.

The BSG and AlOx reactors provided equally satisfactory yields of **3aa** at 120 °C in the model reaction (Entries 1 and 2, Table 2), although metal precipitation on the surface as well as particle build-up complicated the use of the AlOx reactor. In the BSG reactor we observed no metal precipitation on the glass, however, some particle build-up was present.

A possible advantage with the use of the CF-MAOS methodology with non-homogeneous reaction systems is that it has been suggested that MW heating may lead to a specific MW effect and assist in the creation of an active interface and promote transport processes between liquid interfaces.^{54–56} By using a SiC reactor (Figure 3) and taking advantage of the fact that SiC absorbs MW irradiation¹⁸ we could mimic conventional heating and thus comment on a potential

MW activated liquid interface^{55,56}. The silicon carbide reactor gave 74% yield of **3aa** at 100 °C (Entry 3). This yield is comparable to the results obtained for the other reactor materials (78% - 79%), providing no support for a non-thermal beneficial MW effect for this process⁵⁷. However, this indicates that the conventional heating option is viable for this reaction.

Next, we initiated a study of the scope and limitations of the CF-MAOS protocol by investigating the reaction of different nitriles with sodium benzenesulfinate (1b) utilizing both BSG and AlOx reactors. The reaction with benzonitrile (2a) furnished **3ba** in 53% and 50% isolated vield using a BSG and AlOx reactor, respectively (Table 3, Entry 1).⁵⁸ Reaction with an alkylnitrile, butyronitrile (2b) gave ketone 3bb with a good yield of 71% / 54% (Entry 2), and the reaction with benzyl cyanide (2c) furnished 79% / 63% yield of 3bc (Entry 3). A heterocyclic functionality could be introduced by employing 3-thiophenecarbonitrile (2d) which gave a satisfying 66% / 58% yield of **3bd** (Entry 4). 4-Bromobenzonitrile (2e) gave only 47% / 56% isolated yield of 3be with the CF-MAOS protocol (Entry 5) but no traces of byproducts from Pd(0)-catalyzed activation of the phenyl bromide functionality was observed. All entries except for the reaction with benzyl cyanide (2c) as the nitrile substrate resulted in lower yield than for the reported batch protocol.³¹ However, batch reactions of **1b** with **2a** and **2e** performed at the same diluted concentrations used for flow applications and resulted in identical outcome as the CF-MAOS protocol (see Supporting Information for details). The yields in Table 3 using the AlOx reactor are generally slightly lower compared to the results obtained using the BSG reactor. Importantly, although no problems with reactor failure resulting from MW induced superheating due to metal precipitation was observed in this study, regardless of reactor material.

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BSG reactors have previously been reported to undergo thermal cracking under MW processing.⁵⁹

Table 3. Pd(II)-Catalyzed Desulfitative Addition Reactions of Sodium Benzenesulfinate to







All reactions were carried out at 100 °C, 120 °C and 140 °C. The highest yielding reaction temperature according to GC-MS was in all cases 120 °C. The temperature was measured using an Optris CSmicro 3M IR sensor for the borosilicate glass (BSG) reactor, and an Optris CT IR

sensor with a LT22 sensing head for the aluminium oxide (AlOx) reactor. ^a Isolated yield. >95% purity according to 1 H NMR.

After the screening of nitrile substrates we decided to evaluate the scope of sodium sulfinates with acetonitrile (**2f**) as the nitrile partner. Aryl sulfinates **1a**, **1b** and **1c** afforded yields of 55%/50%, 61%/58% and 68%/62%, respectively, of the corresponding products **3af**, **3bf** and **3cf** with CF-MAOS processing (Table 4, Entries 1-3). Sodium 4-acetamidobenzenesulfinate (**1d**) gave the corresponding aryl ketone product **3df** in 60%/56% yield (Entry 4) with no trace of the corresponding hydrolyzed product. The short reaction time of the CF-MAOS protocol may explain the results with the more electron-poor sodium 4-bromobenzenesulfinate **1e** which only afforded trace amounts of **3ef** (Entry 5). The same trend with slightly lower yields for reactions carried out in the AlOx reactor was observed.

Table 4. Pd(II)-Catalyzed Desulfitative Addition Reactions of different Sodium Aryl Sulfinates to Acetonitrile



All reactions were carried out at 100 °C, 120 °C and 140 °C. The highest yielding reaction temperature according to GC-MS was in all cases 120 °C except for entry 2. The temperature was measured using an Optris CSmicro 3M IR sensor for the borosilicate glass (BSG) reactor,

and an Optris CT IR sensor with a LT22 sensing head for the aluminium oxide (AlOx) reactor. ^a Isolated yield. >95% purity according to ¹H NMR. ^b Reaction run at 140 °C. ^cAccording to GC-MS.

CONCLUSION

A protocol for CF-MAOS of aryl ketones by Pd(II)-catalyzed addition of sodium aryl sulfinates to nitriles, with a production capacity of up to 4.3 mmol/h, was developed. Though reaction mixtures were biphasic, acceptable to good yields of the desired products were obtained. MW transparent BSG reactors performed well and AlOx reactors were identified as safe alternatives as they are more thermostable and resilient to MW induced superheating due to metal precipitation. The use of a MW absorbing silicon carbide reactor gave comparable results – indicating that no specific MW interaction with the interface between the two phases of the reaction mixture was present.

EXPERIMENTAL SECTION

General information

Palladium catalysts were purchased from Strem Chemicals. All reagents and solvents are commercially available and were used as received. The sodium salts of 4-methylbenzenesulfinic acid (**1a**), benzenesulfinic acid (**1e**) and 4-acetamidobenzenesulfinic acid (**1d**) are commercially available. The other sodium arylsulfinates are known compounds and were prepared using modified literature procedures.^{60,61} All products are known compounds and are commercially available. GC–MS analyses were performed with a CP-SIL 8 CB Low Bleed (30 m × 0.25 mm) capillary column using a 70–300 °C temperature gradient or and EI ionization at 70 eV. Nuclear magnetic resonance (NMR) spectra were recorded on an NMR spectrometer at 400 MHz for ¹H and at 100.5 MHz for ¹³C. Chemical shifts are reported in parts per million and referenced

indirectly to TMS via the residual solvent signals (¹H, CDCl₃ at 7.26 ppm or methanol-d4 at 3.31 ppm; ¹³C, CDCl₃ at 77.16 ppm or methanol-d4 at 49.00 ppm). All final compounds were >95% pure as determined by NMR. For detailed information regarding the CF-MAOS setup, see Supporting Information.

General procedure

 $Pd(O_2CCF_3)_2$ and 6-methyl-2,2'-bipyridyl were weighed and dissolved in THF:H₂O (1:1) to a volume corresponding to approximately 20% of the total reaction volume. Sonication was used to effect dissolution of the catalyst followed by filtration through a 0.45 µm syringe filter to remove any particulates. The aryl sulfinate (1, 75 mM), nitrile (2, 5 equiv) and internal standard (2-methylnaphthalene, 1.0 equiv) were weighed and dissolved in THF:H₂O (1:1) to a volume corresponding to approximately 40% of the total reaction volume, sonicated and added via a 0.45 µm syringe filter to the catalyst solution. TFA (10 equiv) was added and the reaction mixture was diluted in a measuring cylinder to the desired reaction volume (typically 50 mL) by addition of THF:H₂O (1:1). The reaction mixture was stirred vigorously and pumped at a flow rate of 1 mL/min into the MW heated 200 mm long øi 3 mm reactor at a pressure of approximately 40 bar maintained by an adjustable back pressure regulator. After approximately 10 minutes of equilibration, the microwave processed product mixture was collected manually. The collected product mixture was stirred vigorously and 8 mL were quickly measured out by syringe and poured into 30 mL of 2 M NaOH and extracted with 3×50 ml DCM. The organic layers were combined, dried over MgSO₄ and concentrated *in vacuo*. The crude product was purified by column chromatography.

4'-Methyl-2-phenylacetophenone (**3aa**). Synthesized from **1a** and **2a** according to the general procedure. Purification was performed by column chromatography using pentane/dichloromethane as the solvent to give **3aa** as a white solid (100 mg; 79%); ¹H NMR (400 MHz, CDCl₃) δ = 8.09 – 7.82 (m, 2H), 7.51 – 7.13 (m, 7H), 4.26 (s, 2H), 2.40 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ = 197.4, 144.1, 134.9, 134.3, 129.6, 129.5, 128.9, 128.8, 126.9, 45.6, 21.8.

Benzophenone (**3ba**): Synthesized from **1b** and **2a** according to the general procedure. Purification was performed by column chromatography using pentane/dichloromethane as the solvent to give **3ba** as a colorless oil (58 mg; 53%); ¹H NMR (400 MHz, CDCl₃) δ = 7.86 – 7.77 (m, 4H), 7.63 – 7.56 (m, 2H), 7.53 – 7.44 (m, 4H). ¹³C NMR (101 MHz, CDCl₃) δ = 196.8, 137.7, 132.5, 130.2, 128.4.

Butyrophenone (**3bb**): Synthesized from **1b** and **2b** according to the general procedure. Purification was performed by column chromatography using pentane/dichloromethane as the solvent to give **3bb** as a colorless oil (63 mg; 71%); ¹H NMR (400 MHz, CDCl₃) $\delta = 8.01 - 7.91$ (m, 2H), 7.59 - 7.52 (m, 1H), 7.49 - 7.41 (m, 2H), 2.98 - 2.92 (m, 2H), 1.77 (h, J = 7.4 Hz, 2H), 1.01 (t, J = 7.4 Hz, 3H). ¹³C NMR (101 MHz, CDCl₃) $\delta = 200.5$, 137.2, 133.0, 128.7, 128.2, 40.7, 17.9, 14.0.

Phenyl(thiophen-3-yl)methanone (**3bd**): Synthesized from **1b** and **2d** according to the general procedure. Purification was performed by column chromatography using pentane/dichloromethane as the solvent to give **3bd** as a colorless oil (75 mg; 66%); ¹H NMR (400 MHz, CDCl₃) δ = 7.92 (ddd, J = 2.9, 1.3, 0.5 Hz, 1H), 7.87 – 7.80 (m, 2H), 7.63 – 7.54 (m, 2H), 7.53 – 7.44 (m, 2H), 7.37 (ddd, J = 5.1, 2.9, 0.5 Hz, 1H). ¹³C NMR (101 MHz, CDCl₃) δ = 190.0, 141.4, 138.7, 134.0, 132.4, 129.4, 128.7, 128.5, 126.3.

2-Phenylacetophenone (**3bc**): Synthesized from **1b** and **2c** according to the general procedure. Purification was performed by column chromatography using pentane/dichloromethane as the solvent to give **3bc** as a white solid (93 mg; 79%); ¹H NMR (400 MHz, CDCl₃) δ = 8.08 – 7.99 (m, 2H), 7.61 – 7.52 (m, 1H), 7.52 – 7.42 (m, 2H), 7.39 – 7.22 (m, 5H), 4.30 (s, 2H). ¹³C NMR (101 MHz, CDCl₃) δ = 197.6, 136.6, 134.5, 133.1, 129.4, 128.6, 128.6, 128.6, 126.8, 45.5.

4-Bromobenzophenone (**3be**): Synthesized from **1b** and **2e** according to the general procedure. Purification was performed by column chromatography using pentane/dichloromethane as the solvent to give **3be** as a white solid (74 mg; 47%); ¹H NMR (400 MHz, CDCl₃) δ = 7.81 – 7.74 (m, 2H), 7.71 – 7.57 (m, 5H), 7.55 – 7.45 (m, 2H). ¹³C NMR (101 MHz, CDCl₃) δ = 195.7, 137.3, 136.4, 133.5, 132.8, 131.7, 131.7, 130.1, 128.5, 127.6.

4'-Methylacetophenone (**4af**): Synthesized from **1a** and **2f** according to the general procedure. Purification was performed by column chromatography using pentane/dichloromethane as the solvent to give **4af** as a colorless liquid (40 mg; 55%); ¹H NMR (400 MHz, CDCl₃) δ = 7.87 – 7.83 (m, 2H), 7.27 – 7.23 (m, 2H), 2.56 (s, 4H), 2.40 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ = 197.8, 143.8, 134.7, 129.2, 128.4, 26.5, 21.6.

Acetophenone (**3bf**): Synthesized from **1b** and **2f** according to the general procedure. Purification was performed by column chromatography using pentane/dichloromethane as the solvent to give **3bf** as a colorless oil (49 mg; 61%); ¹H NMR (400 MHz, CDCl₃) δ = 8.08 – 7.84 (m, 2H), 7.57 – 7.52 (m, 1H), 7.48 – 7.41 (m, 2H), 2.59 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) δ = 198.2, 137.2, 133.2, 128.6, 128.4, 26.7.

4-Methoxy-acetophenone (**3cf**): Synthesized from **1c** and **2f** according to the general procedure. Purification was performed by column chromatography using pentane/dichloromethane as the solvent to give **3cf** as a colorless oil (61 mg; 68%); ¹H NMR (400 MHz, CDCl₃) $\delta = 8.11 - 7.71$ (m, 2H), 6.93 (d, J = 9.0 Hz, 2H), 3.87 (s, 3H), 2.55 (s, 3H). ¹³C NMR (101 MHz, CDCl₃) $\delta = 196.9$, 163.6, 130.7, 113.8, 55.6, 26.5.

4'-Acetamidoacetophenone (**3df**): Synthesized from **1d** and **2f** according to the general procedure. Purification was performed by column chromatography using pentane/dichloromethane as the solvent to give **3df** as a white solid (63 mg; 60%); ¹H NMR (400 MHz, Methanol-d4) δ = 7.96 – 7.90 (m, 2H), 7.62 (d, J = 8.4 Hz, 2H), 7.53 (s, 1H), 2.57 (s, 3H), 2.22 (s, 3H). ¹³C NMR (101 MHz, Methanol-d4) δ = 199.4, 171.9, 144.8, 133.7, 130.7, 120.1, 26.4, 24.0.

ASSOCIATED CONTENT

Supporting Information

The supporting information is available free of charge on the ACS Publications website at DOI:

Detailed continuous flow instrument setup and reactor parameters, heating profiles, ¹H NMR and ¹³C NMR spectra for products.

AUTHOR INFORMATION

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Author Contributions

The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

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ABBREVIATIONS

AlOx, aluminium oxide; BSG, borosilicate glass; CF, continuous flow; CF-MAOS, continuous flow microwave assisted organic synthesis; MW, microwave; Pd, palladium; SiC, silicon carbide.

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