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A Scalable Two-Step Continuous Flow Synthesis of Nabumetone and Related 4-Aryl-2-butanones

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ABSTRACT: Three different continuous flow strategies for the generation of important 4-aryl-2-butanone derivatives including the anti-inflammatory drug nabumetone [4-(6-methoxy-2-naphthalenyl)-2-butanone] and the aroma compounds raspberry ketone [4-(4-hydroxyphenyl)-2-butanone] and its methyl ether [4-(4-methoxyphenyl)-2-butanone] were evaluated. All three protocols involve the initial preparation of the corresponding 4-aryl-3-buten-2-ones via Mizoroki−Heck, Wittig, or aldol strategies, which is then followed by selective hydrogenation of the C═C double bond to the desired 4-aryl-2-butanones. The synthetic routes to 4-aryl-3-buten-2-ones were first optimized/intensified on small scale to reaction times of 1−10 min using batch microwave heating technology and then translated to a scalable continuous flow process employing commercially available stainless steel capillary tube reactors. For the synthesis of 4-(4-methoxyphenyl)-3-buten-2-one a further scale-up using a custom-built mesofluidic mini-plant flow system capable of processing several liters per hour was designed to further expand the scale of the process. The final hydrogenation step was performed using a fixed-bed continuous flow hydrogenator employing Ra/Ni as a catalyst.

INTRODUCTION

In the past decade the use of microreactors and continuous flow technology in general has become increasingly utilized in the process chemistry and chemical manufacturing communities.[1−3] An important advantage of microreaction/continuous flow technology compared to conventional batch methods is the ease with which reaction conditions can be scaled—without the need for reoptimization—through the operation of multiple systems in parallel or other techniques (numbering-up, scaling out), thereby readily achieving production-scale capabilities.[3,4]

Historically, most synthetic transformations performed in microreaction devices have involved ambient or even low-temperature conditions in order to safely conduct highly exothermic reactions.[1,2,5] More recently, following the concepts of "Process Intensification" and "Novel Process Windows",[6] flow chemistry at elevated temperature conditions in pressurized continuous flow reactors has been reported, although the number of publications describing synthetically valuable transformations in a genuine high-temperature and high-pressure flow regime is still rather limited.[7] In general, high-temperature chemistry offers many distinct benefits as demonstrated by the recent success of microwave-assisted organic synthesis.[8,9] In microwave chemistry, reaction times can often be reduced from hours to minutes by efficient and rapid dielectric heating of the reaction mixture in a sealed vessel to temperatures far above the boiling point of the solvent under atmospheric conditions.[8,9] The short reaction times experienced in high-temperature microwave chemistry protocols form an ideal basis for continuous flow processing where short residence times are essential in order to achieve a high throughput. Several recent investigations have described the successful translation of high-speed batch microwave protocols into microreactor/continuous flow protocols employing conventionally heated laboratory-scale flow systems where the rapid heating and high-temperature conditions achieved in a microwave reactor could be adequately mimicked (microwave-to-flow paradigm).[10,11]

Herein we report an extension of this concept, demonstrating that conditions optimized under batch microwave conditions on a milliliter scale can be translated to a laboratory-scale microreactor setting typically providing mL/min throughput, and can be further adapted to a mesofluidic flow regime that allows a L/h throughput, therefore more closely resembling pilot-plant/production-scale capabilities. As model systems we have evaluated different continuous flow strategies for the generation of the anti-inflammatory drug nabumetone [4-(6-methoxy-2-naphthalenyl)-2-butanone] and related 4-aryl-2-butanones using a combination of two process-intensified flow reaction steps. The synthetic routes were first optimized on small scale using controlled microwave batch technology and then translated to continuous flow processes employing commercially available stainless steel capillary tube reactors demonstrating "proof-of-concept". Ultimately, a custom-built large-scale mesofluidic flow setup capable of processing 2.7 L/h was designed to significantly expand the scale of the process.

RESULTS AND DISCUSSION

Nabumetone [4-(6-methoxy-2-naphthalenyl)-2-butanone] (**2a**) is a nonsteroidal anti-inflammatory drug (NSAID) developed by Beecham (Smith−Kline−Beecham group) in 1973 and launched in 1985 under a variety of brand names (Relafen, Noracet).[12,13] This drug is generally used to treat pain, inflammation, and other symptoms of osteoarthritis and rheumatoid arthritis. Nabumetone has been shown to be more potent than its

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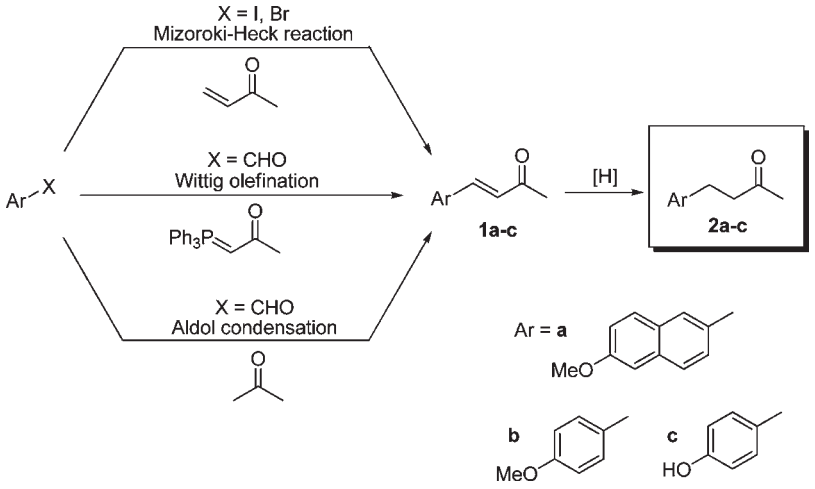
Scheme 1. Different synthetic strategies to 4-aryl-butanones 2a−c



analogues (e.g., Naproxen) and to have a slightly lower risk of gastrointestinal side effects than most other NSAIDs.[13] Its nonacidic nature and pro-drug formulation, together with the lack of biliary secretion of its active metabolite, 6-methoxy-2-naphthylacetic acid, are thought to contribute to the improved gastrointestinal tolerability of this drug.[13]

Two structurally closely related compounds of interest in this family of 4-aryl-2-butanones are 4-(4-methoxyphenyl)-2-butanone (**2b**) and 4-(4-hydroxyphenyl)-2-butanone (**2c**).[14] Both substances are odorous products with raspberry scent obtained by extraction from *Aloe* wood, the latter structure being a primary aroma compound of red raspberries known as raspberry ketone (RK).[14] Apart from its application in flavor and fragrance formulations, raspberry ketone **2c** has been shown to have anti-obesity action[15] and is used as a "cosmeceutical", being a constituent of skin-lightening cosmetics, and weight-loss-advancing dietary supplements.[16] 4-(4-Methoxyphenyl)-2-butanone (**2b**), also known as "raspberry ketone methyl ether", is a component of the essential oil obtained from *Illicium verum* fruits, distributed in the tropical and subtropical zones of Asia, North America, and the Atlantic.[17] This oil is known to have insecticidal activity against Japanese termites and is used as fungicide against post-harvest pathogens.[17] Furthermore, ketone **2b** is a common perfume ingredient that is applied in a variety of consumer products that have malodor control as primary or secondary function (deodorants, detergents, aerosol sprays).[18] As the quantities of ketones **2b**,**c** that can be obtained from natural sources are exceedingly low, synthetic routes for both ketones are in high demand.

Commercially, 4-aryl-2-butanones **2b** and **2c** are generally prepared by Friedel−Crafts alkylation of anisole or phenol with 4-hydroxybutan-2-one or methyl vinyl ketone (MVK) using homogeneous or heterogeneous Lewis or Brønsted acid catalysts.[19] However, a variety of side reactions (i.e., transalkylation, isomerization, polymerization, and polyalkylation) are typically observed in these acid-catalyzed transformations. For this reason, several biotechnological[20] and alternative multistep synthetic strategies[21] have recently been disclosed in the literature for the preparation of raspberry ketone **2c** and its methoxy analogue **2b** (see Scheme 1).

For the industrial preparation of nabumetone (**2a**) various processes have been disclosed that primarily involve the initial preparation of the corresponding unsaturated derivative **1a** followed by hydrogenation of the C=C double bond.[22−26] Two main standard methods have been used for the generation of intermediate **1a**: (1) The Pd-catalyzed Mizoroki−Heck reactions of 2-halo-6-methoxynaphthalene with methyl vinyl ketone (MVK) and related olefins (Hoechst-Celanese[22] and Rhodia Chimie[23]); or (2) the base-catalyzed aldol condensation of 6-methoxy-2-napthaldehyde and acetone (Albermale Corporation).[25] Some of the most efficient general published methods for synthesizing 4-aryl-2-butanones **2a−c** are summarized in Scheme 1. All three protocols (Mizoroki−Heck, Wittig, and aldol reactions) involve the initial preparation of the corresponding 4-aryl-3-buten-2-ones **1a−c** which is then followed by selective hydrogenation of the C=C double bond to 4-aryl-2-butanones **2a−c**.

With the aim of developing process-intensified methods for the rapid synthesis of the key intermediates **1a−c** in a flow format we have initially screened and optimized the above transformations under microwave batch conditions and then adapted these conditions for use in a flow reactor. The final double bond hydrogenation was achieved in a commercially available flow hydrogenation device (H-Cube). The individual synthetic strategies and their suitability for a scalable flow synthesis are evaluated in the following paragraphs.

Mizoroki−Heck Reaction. *Batch Microwave Processing.* Among the many transition metal-catalyzed carbon−carbon bond-forming protocols, the Mizoroki−Heck reaction involving the Pd-catalyzed carbon−carbon coupling of aryl halides with alkenes is well-known.[27,28] During the past decades, proper catalyst/ligand design has led to a variety of very efficient catalytic systems for the Mizoroki−Heck reaction that provide high reaction rates and turnover numbers (TON), and often afford good selectivities and product yields.[28] Notably, Mizoroki−Heck transformations have been reported on an industrial scale.[29]

The starting point for our studies involved the adaptation of the Mizoroki−Heck reaction of methyl vinyl ketone (MVK) with 4-iodoanisol (**3b**) into a high-speed microwave protocol leading to the desired 4-aryl-3-buten-2-one **1b** (Table 1).[30] 4-Iodoanisol (**3b**) was used as a model compound because of its ready availability and low cost. The most favorable reaction conditions described in the patent literature for this and related Mizoroki−Heck couplings involving MVK utilize a combination of a Pd(II) or Pd(0) complexes as catalysts, tertiary amine as base, and an aprotic polar solvent (such as DMF or DMA).[22,23]

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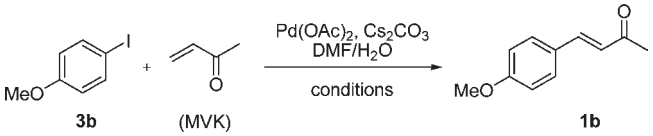
Table 1. Optimization of the Mizoroki−Heck reaction of 4-iodoanisole (3b) and methyl vinyl ketone (MVK) under microwave batch and continuous flow conditions[a]



3b (MVK) 1b

entry	conditions	$Pd(OAc)_2$ [mol %]	MVK [equiv]	T [°C]/t [min]	flow rate [mL/min]	conv [%][b]	product purity [%][c]
1	MW batch	1	1.05	160/20	–	>99	40
2	MW batch	1	1.1	160/20	–	>99	60
3	MW batch	1	1.3	160/20	–	>99	71
4	MW batch	1	1.5	160/20	–	>99	72 (74)[d]
5	MW batch	1	1.5	160/10	–	>99	42
6	MW batch	0.5	1.5	160/20	–	>99	70
7	MW batch	0.2	1.5	160/20	–	>99	74 (76)[d]
8	MW batch	0.1	1.5	160/20	–	84	57
9	MW batch	0.2	1.5	180/10	–	>99	69 (66)[d]
10	flow[a]	0.2	1.5	180/10[e]	1.6	>99	73 (67)[d]

[a] General reaction conditions: 0.4 mmol **3b**, Cs_2CO_3 (1.1 equiv), DMF/H_2O 3:1 (3 mL); single-mode microwave irradiation (hold time, IR temp monitoring). Flow experiments (60 bar pressure) were performed using a ThalesNano X-Cube Flash instrument equipped with a 16-mL stainless steel coil (1 mm i.d.). See the Experimental Section for further information. [b] Conversions refer to HPLC peak area integration at 230 nm. [c] Product purity refers to relative peak area (%) ratios of crude HPLC traces. [d] Isolated yield after flash chromatography. [e] Residence time (flow rate of 1.6 mL/min).

Reported reaction times vary between 2 and 5 h at 120−160 °C, clearly requiring further improvement before continuous flow processing can be considered. The group of Corma has reported immobilized Pd catalysts for the synthesis of 4-aryl-3-buten-2-one **1a**−**c** using similar reaction conditions.[21,24]

In our hands, the Mizoroki−Heck coupling of 4-iodoanisol (**3b**) with MVK proceeded well under controlled microwave conditions. High conversions were typically achieved with 1 mol % of $Pd(OAc)_2$ employing 1.5 equiv of MVK after 20 min at 160 °C in a variety of solvents. Lower reaction temperatures or shorter times led to a diminished yield, less attractive for subsequent flow processing, whereas higher temperatures produced more undesired (i.e., dehalogenated and homocoupling) byproducts. As in a previous report from our group on microwave-assisted and continuous flow Mizoroki−Heck reactions,[31] special attention was paid to the selection of a proper base for this transformation, keeping the general requirement for homogeneous reaction conditions for subsequent translation to a continuous flow process in mind. Different amounts (1.1−1.5 equiv) of various organic and inorganic bases such as pyridine, diazabicycloundecane (DBU), sodium carbonate, sodium hydroxide, sodium hydrogen carbonate, potassium *tert*-butoxide, and cesium carbonate were tested. Subsequently, a variety of solvents including acetonitrile and dimethylformamide (DMF), and solvent mixtures containing varying amounts of water (e. g., DMF/water from 4:1 to 1:4 or *t*-BuOH/water 4:1) were also screened as possible reaction media. Different loadings of the $Pd(OAc)_2$ catalyst were examined, as well as varying amounts of MVK for a range of temperature/time conditions (Table 1).

From this matrix we were able to identify the optimal set of conditions which worked best in a small-scale microwave batch environment (0.4 mmol) and fulfilled the criteria of reaction homogeneity throughout the overall process: DMF/water (3:1) as a solvent mixture, 0.2 mol % $Pd(OAc)_2$ as a catalyst, 1.5 equiv of MVK and 1.1 equiv of Cs_2CO_3 as a base (Table 1, entry 7). Applying these conditions at 160 °C (10−12 bar) for 20 min, the desired 4-aryl-3-buten-2-one **1b** was obtained in 76% isolated yield after purification by flash chromatography. It should be noted that somewhat higher isolated yields (80−90%) can be obtained by applying Na_2CO_3 as base in combination with higher catalyst loadings (1 mol %), but these conditions were not homogeneous and thus unsuitable for continuous flow processing.

In our hands, use of the corresponding bromo precursors[22,23] required higher reaction temperatures and provided lower product yields and selectivities; therefore, this route appeared unsuitable for continuous flow processing and was pursued no further. The optimized conditions (Table 1, entry 7) were also applied to the analogous coupling involving 4-iodophenol (**3c**) providing 4-(4-hydroxyphenyl)-3-buten-2-one (**1c**) in 78% yield.

To rapidly evaluate whether the enhancements seen in the microwave-assisted reactions are the results of a purely thermal phenomenon or whether specific/nonthermal microwave effects are involved, we compared the outcome obtained using both microwave-transparent Pyrex and strongly microwave-absorbing silicon carbide (SiC) vials, in combination with a single-mode microwave reactor that allows simultaneous temperature monitoring by external infrared (IR) and internal fiber-optic probes (FO).[32,33] For the example presented herein (same conditions shown in Table 1, entry 7), virtually identical results in terms of conversion, purity profile, and/or product yields were obtained using both Pyrex and SiC vials, thus confirming that the electromagnetic field has no direct influence on the reaction pathway and that this procedure could therefore be easily mimicked in a conventionally heated flow system.[32]

Continuous Flow Processing. Continuous-flow experimentation on the Mizoroki−Heck reaction was performed in a high-temperature, high-pressure microtubular flow unit that can be used for processing homogeneous reaction mixtures (X-Cube Flash, Thales Nanotechnology Inc.).[34] The reactor uses stainless steel coils (i.d. 1000 μm) of variable length (4-, 8-, and 16-mL volume) that can be directly heated across their full length by

electrical resistance heating to temperatures up to 350 °C. The reaction mixture is introduced to the reactor block containing the steel coils and heat exchanger via one or more standard HPLC pumps (flow rate 0.01−10.0 mL/min). The system pressure valve stabilizes the set pressure value between a pressure range of 50−180 bar.[32]

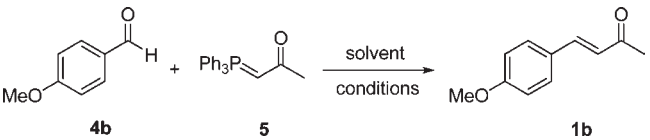
Employing the flow reactor system, the batch microwave conditions shown in Table 1, entry 9 (180 °C, 10 min) were used. Similar to our earlier experiences in flow Mizoroki−Heck chemistry,[31] using the 16-mL stainless steel coil, a temperature of 180 °C and flow rate to 1.6 mL/min (10 min residence time), full conversion was observed providing a 67% isolated yield of the desired 4-(4-methoxyphenyl)-3-buten-2-one (**1b**). Although successful, due to the comparatively low selectivity achieved in this Mizoroki−Heck coupling and the required product purification of the crude reaction mixture, and in consideration of the high costs of catalyst and starting materials (aryl iodides) it was decided not to further pursue this avenue on scale.

Wittig Reaction. *Batch Microwave Processing.* As a second synthetic strategy to access the key intermediates **1a**−**c**, the Wittig olefination of aldehydes **4a**−**c** in the presence of (acetylmethylene)triphenylphosphorane (**5**) was investigated (Scheme 1). The Wittig reaction is a strategic, widely applicable carbon−carbon double bond-forming process.[35] Traditional olefination reaction conditions generally include a stabilized ylide and an aldehyde, often in solvents ranging from hexane to DMF or dimethylsulfoxides. It is known that, under conventional conditions, the reaction time of stabilized ylides with aromatic aldehydes is generally long and it is strongly affected by the aromatic substitution pattern, especially when nonpolar solvents are employed.[35] Notably, Wittig reactions of ketones or aldehydes with stabilized organophosphorus reagents under microwave conditions are comparatively rare,[36,37] and only very recently a Wittig reaction under phase-transfer conditions has been demonstrated utilizing continuous-flow conditions.[37] A previous study by Cereda involving a domestic microwave oven has described the Wittig olefination of *p*-anisaldehyde (**4b**) and (acetylmethylene)triphenylphosphorane (**5**) using DMSO as a solvent.[36] In our hands, employing aldehyde **4b** and 1.5−1.7 equiv of phosphorane **5** in MeCN (10−12 bar) or DMF (12−14 bar) at temperatures of 190−210 °C, high conversions were achieved under microwave conditions within 10−20 min (Table 2). Although MeCN behaved well as solvent, truly homogeneous reaction conditions were only obtained in DMF up to concentrations of 0.1 M. Therefore, the conditions reported in Table 2, entry 6 were selected as optimal conditions for both batch and continuous flow processing (see Table 3). This efficient and clean Wittig olefination protocol was thus also applied to the synthesis of 4-(6-methoxynaphthalen-2-yl)-3-buten-2-one (**1c**) and 4-(4-hydroxyphenyl)-3-buten-2-one (**1a**), providing the desired products in high yield (Table 3).

As already demonstrated for the Mizoroki−Heck reaction above, careful control experiments using both Pyrex and silicon carbide (SiC) reaction vials were performed in a dedicated microwave reactor using the conditions specified in Table 2 (entry 6) for substrate **4b** to exclude the existence of any nonthermal microwave effects.[32]

Continuous Flow Processing. Having performed the initial time/temperature optimization study on the Wittig olefination under microwave batch conditions, the next step was the translation of these reaction conditions to a continuous flow process. The experimental setup for this particular transformation involved the use of the Uniqsis FlowSyn device.[39] Applying the same reaction conditions as optimized for the microwave batch experiments (see Table 3), full conversions were achieved in all three cases using a 10-mL stainless steel coil heated to 210 °C at a 1 mL/min flow rate (10 min residence time). The desired 4-aryl-3-buten-2-ones **1a**−**c** were obtained in very high isolated yield after flash chromatographic purification (97−98%).

Table 2. Reaction optimization for the Wittig reaction of *p*-anisaldehyde (4b) and (acetylmethylene)triphenylphosphorane (5) under microwave batch conditions[a]

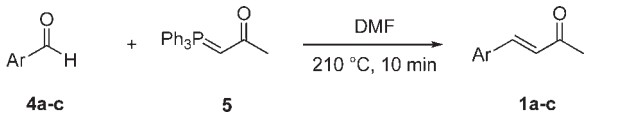


4b **5** **1b**

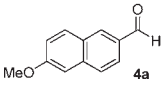
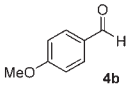
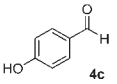
entry	5 [equiv]	temp [°C]/time[min]	solvent	conversion [%][b]
1	1.5	190/20	MeCN	94
2	1.5	200/20	MeCN	98
3	1.7	200/20	MeCN	100 (94)[c]
4[d]	1.7	200/20	DMF	97
5[d]	1.7	210/20	DMF	99 (95)[c]
6[d]	1.7	210/10	DMF	99 (96)[c]

[a] General reaction conditions: 0.4 mmol **4b**, 1.5−1.7 equiv of **5**, 3 mL of solvent, single-mode microwave irradiation, IR temperature control. See the Experimental Section for further information. [b] HPLC peak area integration at 230 nm. [c] Isolated yields using flash chromatography. [d] Homogeneous reaction conditions.

Table 3. Comparison between microwave batch and continuous flow conditions in the Wittig reaction of aldehydes 4a−c with (acetylmethylene)triphenylphosphorane (5)[a]



4a-c **5** **1a-c**

Substrate	Condition	Flow rate [mL/min]	Conversion [%][b]	Yield [%][c]
 **4a**	batch	-	> 99	94
	flow	1	> 99	97
 **4b**	batch	-	> 99	95
	flow	1	> 99	97
 **4c**	batch	-	> 99	70
	flow	1	> 99	98

[a] General reaction conditions: **4a**−**c** (0.1 M), **5** (1.7 equiv), 3 mL (batch)/10 mL (flow) DMF. Batch experiments were carried out using single-mode microwave irradiation. Flow experiments were performed in a Uniqsis FlowSyn instrument using a 10-mL stainless steel coil (1 mm i.d.). See the Experimental Section for further information. [b] HPLC peak area integration at 230 nm. [c] Isolated yields using flash chromatography.

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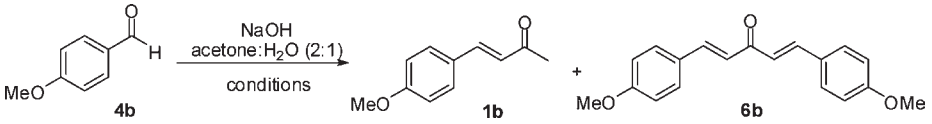
Table 4. Reaction Optimization for the Microwave-assisted Aldol Reaction of *p*-Anisaldehyde (4b) with Acetone[a]



entry	acetone [equiv]	temperature [°C]	time [min]	conversion [%][b]	product distribution **4b**/**1b**/**6b** [%][b]
1	1.4	100	15	79	21/55/16
2	2.75	100	15	98	2/77/19 (88)[c]
3	2.75	70	30	94	6/85/8
4	5.5	70	30	>99	0/94/6
5	11	70	15	>99	0/95/5 (98)[c]
6	11	90	15	97	3/88/9
8	11	90	10	97	3/87/10
9	11	120	10	93	7/80/13
10	11	120	5	95	5/85/10
11	11	120	1	>99	0/93/7(94)[c]

[a] General reaction conditions: 2.5 mmol **4b**, NaOH (0.06 equiv), 3 mL of solvent, single-mode microwave irradiation. See the Experimental Section for further information. [b] HPLC peak area integration at 230 nm. [c] Isolated yields of **1b** using flash chromatography.

The optimized batch and flow Wittig olefinations for the synthesis of the key 4-aryl-3-buten-2-one intermediates **1a**−**c** described herein provide very high selectivity and isolated product yields. Nevertheless, from the standpoint of process chemistry, the use of an expensive organophosphorous reagent (atom economy), and the generation of stoichiometric amounts of triphenylphosphine oxide byproduct are clearly not suitable for a production route.

Aldol Reaction. *Batch Microwave Processing.* The aldol condensation is one of the best-known and most widely used methods for generating carbon−carbon bonds.[40] The reaction involves the condensation of aldehydes with C−H acidic carbonyl compounds (i.e., ketones). Under traditional aldol condensation conditions involving a basic reaction medium, dimer, polymer, and self-condensation products are often formed.[40] Recently, improved methods have been reported for aldol condensations of this type, including methods for the synthesis of the key raspberry ketone and nabumetone precursors **1a**−**c**.[41] In 1999 Kad and co-workers described a microwave-assisted (domestic microwave oven) aldol condensation for the synthesis of the raspberry ketone precursor **1c** from the corresponding aldehyde and acetone using aqueous NaOH.[42] Aldol condensations in continuous flow regimes have scarcely been reported.[43]

In view of our interest to develop economic and efficient synthetic strategies for the preparation of raspberry ketones **2b**,**c** and nabumetone (**2a**) on an industrial scale, we focused our attention on the aldol route (Scheme 1), which apart from the readily available aryl aldehyde precursors **4a**−**c** only requires acetone and an inorganic base as starting materials.[25,41,42] As described above for the Mizoroki−Heck and Wittig pathways, our initial approach was to optimize the reaction to the shortest possible reaction time using a microwave batch approach on small scale. Employing anisaldehyde (**4b**) as starting material full conversion was achieved using 0.06 equiv of NaOH (10% aqueous solution) at 120 °C (9 bar) within one minute (Table 4, entry 11). In these reactions a 2:1 acetone/water mixture was used as solvent, representing an 11-fold molar excess of acetone. These conditions provided high selectivity for the desired mono-aldol condensation product **1b** (93:7). Trying to lower the acetone amount in the reaction mixture resulted in increased levels of double aldol addition which was manifested in the formation of byproduct **6b** (Table 4, entries 1−4). Lowering the reaction temperatures resulted in prolonged reaction times (10−30 min) in order to still achieve full conversions (entries 5−8). Therefore, the completely homogeneous conditions reported in Table 4, entry 11 were chosen to be applied for the continuous flow approach (see below).

Because of reactivity and solubility issues, and the acidic phenolic group in aldehyde **4c**, modified reaction conditions had to be chosen for aldol condensations involving aryl aldehydes **4a** and **4c**, which nevertheless provided high isolated product yields (see Table 5).

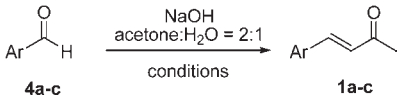
Control experiments using both Pyrex and silicon carbide (SiC) vials in a dedicated single-mode microwave reactor again demonstrated that the short reaction times achieved in the microwave experiments were a result of a purely thermal effect.[32]

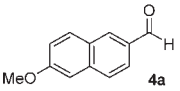
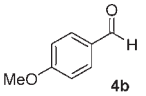
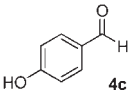
Continuous Flow Processing. The experimental setup for the aldol condensation involved the use of the Uniqsis FlowSyn device, similarly to the case of the Wittig reaction described above.[39] Employing the flow reactor system we initially performed the aldol reaction applying the optimized microwave conditions for the synthesis of **1b** from *p*-anisaldehyde (Table 4, entry 11) using a single-feed concept. Using a 5-mL stainless steel reaction coil, a 5 mL/min flow rate (1 min residence time), and 120 °C temperature allowed the successful processing of a freshly prepared reaction mixture (0.7 M) and the isolation of the desired product**1b** in 90% yield (Table 5, **4b**/flow). As the aldol condensation proceeds also very slowly at room temperature, freshly prepared reaction mixtures were used.

For the synthesis of 4-aryl-3-buten-2-ones **1a** and **1c** a 10-mL stainless steel coil in combination with a 1.34 mL/min flow rate was utilized to ensure the required residence time of 450 s at 70 °C. In the case of naphthylaldehyde **4a** the concentration had to be lowered to 0.1 M because of solubility issues. Nevertheless, full conversion and a high isolated yield of the corresponding aldol condensation product **1a** was obtained (94%).

In these flow experiments, two different strategies to process the reaction mixture were evaluated. In the "one-feed" concept

Table 5. Reaction optimization for the aldol reaction of acetone with aldehydes 4a−c under microwave batch and continuous flow conditions[a]



Substrate	Condition	Temp [°C] /time [s]	Flow rate [mL/min]	Conversion [%][b]	Yield [%][c]
 4a	batch (0.8 M)	70/450	-	> 99	97
	flow (0.1 M)[d]	70/450	1.34	> 99	94
 4b	batch (0.7 M)	120/60	-	> 99	94
	flow (0.7 M)[e]	120/60	5	> 99	90
 4c	Batch (0.6 M)[d]	70/450	-	80	69
	Flow (0.6 M)[d,f]	70/450	1.34	85	78

[a] General reaction conditions: **4a−c** (0.1−0.8 M), NaOH (0.06 equiv), acetone/water 2:1. Batch experiments were carried out using a single-mode instrument (IR temperature sensor). Flow experimentation was performed in a Uniqsis FlowSyn device. See the Experimental Section for further information. [b] HPLC peak area integration at 230 nm. [c] Isolated yield after flash chromatography. [d] 10-mL stainless steel coil (1 mm i.d.). [e] 5-mL stainless steel coil (1 mm i.d.). [f] 2 equiv of NaOH, 1:1 acetone/water.

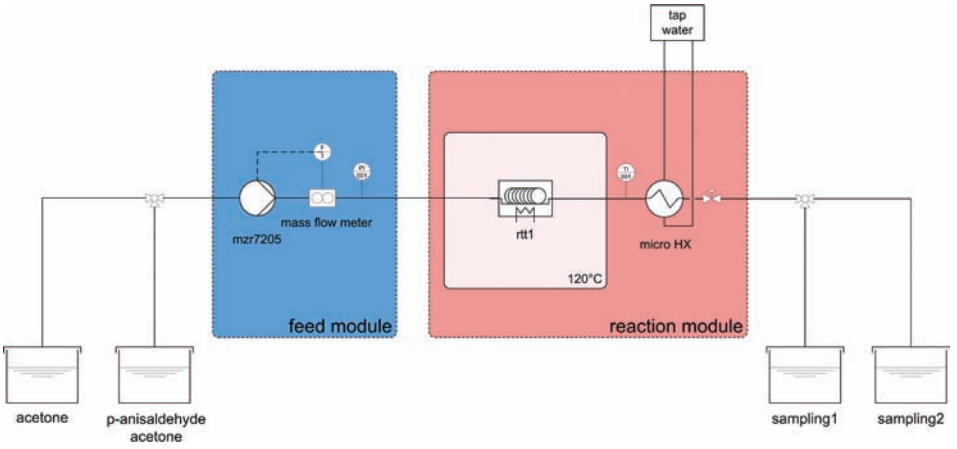


Figure 1. Schematic representation of the mesofluidic flow setup.

the freshly prepared cold reaction mixture (a slow aldol condensation occurs also at room temperature) was pumped through the coil, while in the "two-feed" concept the organic stream (containing aldehyde **4** dissolved in acetone) was pumped separately and mixed with the aqueous stream (containing aqueous NaOH) using the built-in T-mixer in the FlowSyn reactor. Using two different flow rates (3.3 mL/min and 1.7 mL/min, respectively) the desired acetone/water ratio (2:1) and concentration of NaOH base was ensured. In both cases, full conversion and good yields were obtained (see Experimental Section for further information). Assuming a one hour processing time for the aldol condensation of *p*-anisaldehyde (**4b**) and acetone at 120 °C and 1 min residence time (Table 5) a throughput of ~40 g of **1b** per hour can be calculated.

Large-Scale Flow Aldol Condensation. In order to demonstrate the scalability of the flow reaction conditions obtained in a laboratory-scale microreactor using steel coils of 1000 μm i.d. (5−10 mL internal volume) to larger scales more similar to those used in a pilot or production setting we have additionally performed the aldol condensation of *p*-anisaldehyde (**4b**) and acetone shown in Table 5 in a mesofluidic flow setup. This setup allows a larger throughput and provides a first indication for scale up to production scale levels. In this first step a scaling factor of ~10 is adopted. The experiments in the FlowSyn reactor revealed that the "one-feed" concept did show comparable results to the "two-feed" strategy. Therefore, the mesofluidic flow setup followed the "one-feed" concept. Essential parameters for the reaction outcome are temperature control and residence time. Important for further scale up is the control of the flow regime in the residence time zone. Following these requirements, the mesofluidic flow setup was designed of one feed module and one reaction module. A flow mini-plant system of this type enables a multipurpose functionality to continuous flow synthesis plants.[44,45] A schematic representation of the setup used in this work is shown in Figure 1.

The feed module consists of a microannular gear pump (mzr-7205), a Coriflow mass flow meter and a piezosensitive pressure

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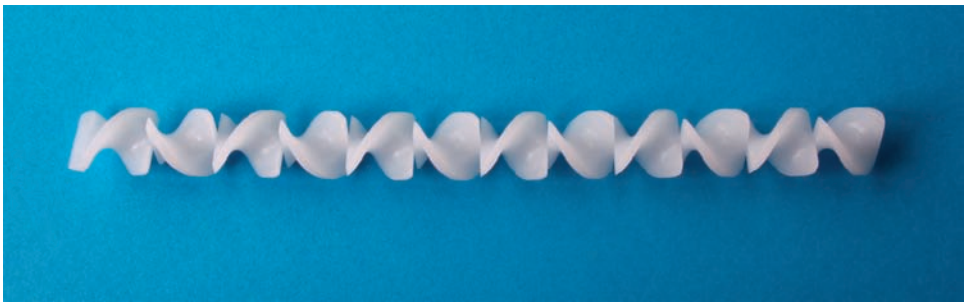
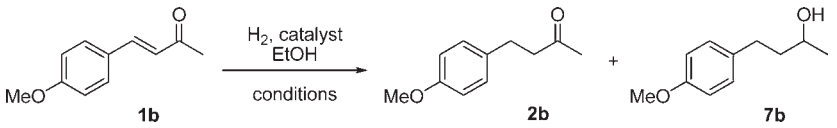


Figure 2. Detailed view of the Teflon static mixing elements (ESSKA.de GmbH).

Table 6. Influence of catalyst, temperature, and flow rate on the flow hydrogenation of 4-aryl-3-buten-2-ones 1b[a]



					conv [%][b]		
entry	conc [M]	flow rate [mL/min]	temp[°c]	catalyst	**1b**	**2b**	**7b**
1	0.5	1.5	70	Pd/C	0	>99	0
2	0.5	2	70	Pd/C	0	>99	10
3	0.7	1	70	Pd/C	0	93	7
4	0.5	1.5	70	Pd/Al_2O_3	47	5	48
5	0.5	1.5	70	Rh/C	87	13	0
6	0.5	1.5	70	Pt/C	0	95	5
7	0.5	1.5	70	Ra/Ni	0	37	64
8	0.5	1.5	r.t.	Ra/Ni	0	>99 (94)[c]	0
9	0.7	1.5	r.t.	Ra/Ni	10	90	0

[a] H-Cube, Full-H_2 mode at atmospheric pressure, substrate in EtOH, 30 mm × 4 mm i.d. catalyst cartridge, ~150 mg of catalyst. [b] Determined by GC/MS (peak area %). [c] Isolated yield.

sensor. The automation of the feeding is done within the MPDS software as developed at Microinnova to control lab plant systems.[45] The reaction module consists of a Teflon residence time tubing (~1 m length) with 8 mm inner diameter and filled with Teflon mixing elements, in addition to a micro heat-exchanger and a pressure maintaining valve. The static mixing elements (Figure 2) allow plug flow behavior, good mixing, and heat transfer along the residence time zone and a reproducible flow regime, which is important for scale-up. A valve on the low-pressure side allows switching between different sampling flasks. The inner volume of the residence time tubing (~50 mL) allows 66 s residence time at 45 mL/min flow rate. This time is slightly elongated compared to that of the FlowSyn reactor experiments, as the inferior surface-to-volume ratio in the larger setup leads to longer time for bringing the reaction mixture to reaction temperature. The residence time tubing is situated in a silicon oil bath. The micro heat-exchanger at the end of the residence time tubing allows exact control of the reaction time, as the reaction mixture is immediately quenched to room temperature.

The overall flow rate in the experiments was 2.4 kg/h, which corresponds to a product flow of 0.35 kg/h. In 104 min 4.65 L reaction mixture were processed at 120 °C. The throughput in this case was limited by the given reaction time. On the same system without any scaling issues the throughput can be raised by a factor of 5 simply by elongating the residence time tubing. A product flow rate of about 1.75 kg/h would be accessible this way.

Hydrogenation. For the selective reduction of the double bond in 4-aryl-3-buten-2-ones **1a**−**c**, we have investigated a continuous-flow hydrogenation protocol employing a fixed-bed catalyst enabling heterogeneous hydrogenations at temperatures up to 100 °C and 100 bar of hydrogen pressure (H-Cube, Thales Nanotechnology Inc.).[46,47] The flow hydrogenation of model substrate **1b** was initially optimized using catalyst cartridges filled with Pd/C, RaNi, Pd/Al_2O_3, Pt/C, or Rh/C using ethanol as a reaction solvent. Although Pd/C as well as Pt/C gave promising results, ultimately only Ra/Ni provided high selectivity for the double-bond hydrogenation at room temperature (Table 6, entry 10). Applying 1.5 mL/min as flow rate at room temperature prevented the formation of the alcohol **7b** as a side product and provided 4-aryl-2-butanones **2b** (raspberry ketone methyl ether) in 94% isolated yield. A preliminary attempt to selectively generate alcohol **7b** remained unsuccessful even at elevated temperatures (70 °C, Table 6, entry 9).

Having established the optimum flow hydrogenation conditions for the model substrate **1b**, we were interested in investigating the synthesis of the other substrates using the same flow hydrogenation conditions. Although our initial flow experiments involved EtOH as the solvent, the comparatively low solubility of **1b** and **1c** in this solvent led us to utilize DMF for these substrates

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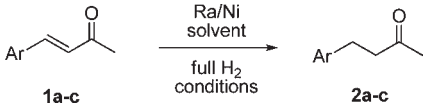
Table 7. Optimized reaction conditions for the flow hydrogenation of 4-aryl-3-buten-2-ones 1a−c[a]



1a-c 2a-c

substrate	solvent	conc [M]	flow rate [mL/min]	temp [°C]	conv [%][b]	yield [%][c]
1a	DMF	0.5	1	100	>99	90
1b	EtOH	0.5	1.5	25	>99	94
1c	DMF	0.7	1	35	>99	91

[a] H-Cube, Full-H_2 mode at atmospheric pressure, substrate in EtOH or DMF, 30 mm × 4 mm i.d. catalyst cartridge, ~150 mg catalyst. [b] Determined by GC/MS (peak area %). [c] Isolated product yield after flash chromatography.

and, as a consequence, to change the reaction conditions (Table 7). In the case of **1c**, clean hydrogenation was observed by using a 0.7 M stock solution (DMF) at a flow rate of 1 mL/min at 35 °C. Similarly, for the synthesis of **2a**, a 90% isolated yield was achieved by using the same catalyst (Ra/Ni) and the same flow rate (1 mL/min, 0.5 M concentration) at 100 °C.

Ultimately, the two individually optimized flow steps (aldol and hydrogenation) had to be merged into one process which required reoptimization of the flow hydrogenation using the basic acetone/water product stream obtained in the aldol condensation.[48] Taking the hydrogenation of 4-(4-methoxyphenyl)-3-buten-2-one intermediate **1b** as an example (at 0.7 M concentration),[49] this required increasing the hydrogenation temperature to 55 °C and adjusting the flow rate to 1 mL/min. Under these conditions an overall 93% crude product yield of raspberry ketone methyl ether **2b** was obtained (75% after chromatographic purification). Although the H-Cube flow hydrogenator is not designed for large scale applications, a number of industrial scale flow hydrogenation devices have recently been described in the literature[47] that would allow coupling the two flow processes (aldol condensation and hydrogenation) effectively on large scale.

CONCLUSIONS

In summary, using the synthesis of 4-aryl-2-butanones **2a**−**c** as model transformations, we have demonstrated that small scale microwave batch processing is a useful tool to optimize reaction conditions for achieving high product yields and selectivities in the shortest possible reaction times. The resulting time−temperature histories were easily translated to conventionally heated high-temperature continuous flow reactors using 1000 μm i.d. stainless steel coils. Because of the high surface-to-volume ratio in these type of microreactors, rapid heat transfer to and from the reaction mixture can be attained (heat exchange), therefore closely mimicking the situation of a small scale microwave experiment. Using appropriate static mixers in connection with a mesofluidic tubular reactor, the conditions obtained from laboratory scale instruments can be directly scaled by a factor of ~10 without reoptimization of conditions. As demonstrated for the synthesis of 4-(4-methoxyphenyl)-3-buten-2-one (**1b**), a throughput of 0.35 kg product per hour can easily be obtained using this technique.

EXPERIMENTAL SECTION

General. ^{1}H NMR spectra were recorded on a Bruker 300 MHz instrument. Chemical shifts (δ) are expressed in ppm downfield from TMS as internal standard. The letters s, d, t, q and m are used to indicate singlet, doublet, triplet, quadruplet and multiplet. GC/MS (FOCUS-GC/DSQ II MS, ThermoFischer) monitoring was based on electron impact ionization (70 eV) using a HP/5MS column (30 m × 0.250 mm ×0.025 μm). After 1 min at 50 °C the temperature was increased in 25 °C/min steps up to 300 °C and kept at 300 °C for 1 min. The carrier gas was helium and the flow rate 1.0 mL/min in constant-flow mode. The identity of the peaks in the chromatograms was confirmed by computerized comparison with the NIST library. Low-resolution mass spectra were obtained on a Shimadzu LCMS-QP 2020 instrument using electrospray ionization (ESI) in positive or negative mode. The preanalysis was carried out on a C18 reverse-phase (RP) analytical column (150 mm × 4.6 mm, particle size 5 μm) at 25 °C using a mobile phase A [water/acetonitrile 90:10 (v/v) + 0.1% TFA] and B (MeCN + 0.1% trifluoroacetic acid (TFA)) at a flow rate of 0.6 mL/min. The following gradient was applied: linear increase from solution 30% B to 100% B in 15 min, hold at 100% solution B for 2 min. All chemicals, solvents or catalysts were obtained from Aldrich Chemical Co. or Alpha Aesar and were used without further purification. Chromatographic purification was done on an automated flash-chromatography system (SP1™, Biotage) using cartridges packed with KP-SIL, 60 Å (40−63 μm particle size) and ethyl acetate/petroleum ether mixtures as eluents. All synthesized compounds are literature known and were characterized by melting point, ^{1}H NMR and LC/MS or GC/MS analysis.

Microwave and Continuous Flow Equipment. Microwave irradiation experiments were carried out in Pyrex or silicon carbide (SiC) process vials in an Anton Paar Monowave 300 single-mode microwave instrument (IR and/or internal fiber-optic temperature monitoring).[32,33] Laboratory scale flow experiments were performed using a FlowSyn (Uniqsis),[39] or X-Cube Flash/H-Cube (ThalesNano Nanotechnology Inc.)[34,47] flow reactors. A detailed description of these instruments and their handling in flow experiments can be found elsewhere.[32,39,46]

4-(6-Methoxynaphthalen-2-yl)-3-buten-2-one (1a). *Batch Microwave Synthesis: Wittig Reaction (Table 3).* To a solution of (acetylmethylene)triphenylphosphorane (**5**, 0.61 mmol, 195 mg, 1.7 equiv) in 3 mL of DMF, 67 mg of 6-methoxy-2-naphthaldehyde (**4a**, 0.36 mmol) were added, and the mixture was stirred for 30 s in a 10-mL Pyrex vial. The solution was capped with a Teflon septum and heated by microwave irradiation at 210 °C for 10 min. After cooling the vessel to ambient conditions, the crude reaction mixture was concentrated under reduced pressure and transferred to a silica-samplet, dried for 1 h at 50 °C in a drying oven, and subjected to automated flash chromatography with petroleum ether/ethyl acetate (0 to 45% gradient) as eluent to provide 76 mg

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(94%) of 4-(6-methoxynaphthalen-2-yl)-3-buten-2-one (**1a**). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.41 (s, 3H), 3.94 (s, 3H), 7.69 (d, J = 16.2 Hz, 1H), 7.19−7.13 (m, 2H), 7.89−7.63 (m, 5H); MS (pos. ESI): m/z = 227 (M^+); mp 118−120 °C, lit.[13a] mp 120−121.

Batch Microwave Synthesis: Aldol Reaction (Table 5). To a solution of 6-methoxy-2-naphthaldehyde (**4a**, 2.50 mmol, 559 mg) in 2 mL of acetone, 60 μL of NaOH 10% solution and 1 mL of distilled water were added, and the mixture was stirred for 30 s in a 10 mL Pyrex vial. The solution was capped with a Teflon septum and heated by microwave irradiation at 70 °C for 450 s. After cooling the vessel to ambient conditions, the crude reaction mixture was concentrated under reduced pressure and transferred to a silica-samplet, dried for 1 h at 50 °C in a drying oven, and subjected to automated flash chromatography with petroleum ether/ethyl acetate (0 to 45% gradient) as eluent to provide 549 mg (97%) of 4-(6-methoxynaphthalen-2-yl)-3-buten-2-one (**1a**) identical in all respects to the sample prepared above.

Continuous Flow Synthesis: Wittig Reaction (Table 3). To a solution of (acetylmethylene)triphenylphosphorane (**5**, 2.04 mmol, 649 mg, 1.7 equiv) in 10 mL of DMF, 6-methoxy-2-naphthaldehyde (**4a**, 223 mg, 1.20 mmol) was added, and the mixture was stirred for 30 s in a 15-mL Pyrex vial. At the same time the FlowSyn reactor was equipped with a stainless steel reaction coil (10 mL volume, 10 min residence time at 1 mL/min flow rate). The reaction parameters, temperature (210 °C) and 1 mL/min flow rate, were selected on the flow reactor, and processing was started, whereby initially only DMF solvent was pumped through the system until the instrument had achieved the desired reaction parameters and stable processing was achieved. At that point the inlet tube was switched from the solvent flask to the 15-mL glass vial containing the reaction mixture. After processing through the flow reactor, the inlet flow was dipped back into the flask containing solvent and was processed for an additional 1 min, thus washing from the system any remaining reaction mixture. The reaction was concentrated under vacuum, and the product, 4-(6-methoxynaphthalen-2-yl)-3-buten-2-one (**1a**), was isolated as described above in 97% identical in all respects to the sample prepared above.

Continuous Flow Synthesis: Aldol Reaction (Table 5). To a solution of 6-methoxy-2-naphthaldehyde (**4a**, 1.37 mmol, 255 mg) in 6.5 mL of acetone were added 33 μL of a 10% aqueous NaOH solution and 3.5 mL of distilled water, and the mixture was stirred for 30 s. At the same time the FlowSyn reactor was equipped with a stainless steel reaction coil (10 mL volume, 450 s residence time at 1.34 mL/min flow rate). The reaction parameters, temperature (70 °C) and 1.34 mL/min flow rate, were selected on the flow reactor, and processing was started, whereby initially only solvent acetone was pumped through the system until the instrument had achieved the desired reaction parameters and stable processing was achieved. At that point the inlet tube was switched from the solvent flask to the 15-mL glass vial containing the freshly prepared reaction mixture (a slow aldol condensation occurs also at room temperature). After processing through the flow reactor, the inlet flow was dipped back into the flask containing solvent and processed for an additional min, thus washing from the system any remaining reaction mixture. The reaction was concentrated under vacuum, and the product, 4-(6-methoxynaphthalen-2-yl)-3-buten-2-one (**1a**), was isolated as described above in 94% yield, identical in all respects with a sample prepared above.

4-(6-Methoxynaphthalen-2-yl)-butan-2-one (2a). A 10-mL stock solution of 4-(6-methoxynaphthalen-2-yl)-3-buten-2-one (**1a**) of 0.5 M concentration in DMF was prepared in a glass vial. The reaction parameters (Full-H_2 mode, 100 °C and 1 mL/min flow rate) were selected on the H-Cube hydrogenator. The instrument was fitted with a 30 mm Ra/Ni CatCart and the processing was started, whereby initially only pure solvent was pumped through the system until the instrument had achieved the desired reaction parameters and stable processing was achieved. At that point the sample inlet line was switched to the vial containing the substrate. A total reaction volume of 15 mL was collected and the cartridge subsequently washed with pure solvent for 5 min to remove any substrate/product still adsorbed on the catalyst. Evaporation of the solvent afforded 4-(6-methoxynaphthalen-2-yl)-butan-2-one (**2a**) as a colorless oil (97% crude yield), which was purified by flash chromatography to provide 1.02 g of pure **2a** as a white solid (90%).^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.15 (s, 3H), 2.81−2.86 (m, 2H), 3.00−3.05 (m, 2H), 3.91 (s, 3H), 7.11−7.68 (m, 6H); MS (pos. ESI): m/z = 229 (M^+); mp 77−79 °C, lit.[13a] mp 80−81 °C.

4-(4-Methoxyphenyl)-3-buten-2-one (1b). *Batch Microwave Synthesis: Mizoraki−Heck Reaction (Table 1).* To 1 mL of DMF/H_2O (3:1) solvent in a 10 mL Pyrex microwave vial 4-iodoanisole (**3b**, 0.43 mmol, 100 mg), methyl vinyl ketone (0.64 mmol, 52 μL, 1.5 equiv) and Cs_2CO_3 (0.47 mmol, 154 mg, 1.1 equiv) were added, followed by 2 mL of a 0.0004 M stock solution of $Pd(OAc)_2$ in DMF/H_2O (3:1) (0.19 mg, 0.2 mol %). The reaction mixture was stirred for 30 s, capped with a Teflon septum and subjected to microwave heating for 20 min (hold time) at 160 °C. After cooling to ambient temperature, the crude reaction mixture was concentrated under reduced pressure and the residue subjected to automated flash chromatography with petroleum ether/ethyl acetate (0 to 45% gradient) as eluent to provide 56 mg (74%) of 4-(4-methoxyphenyl)-3-buten-2-one (**1b**). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.36 (s, 3H), 3.85 (s, 3H), 6.61 (d, J = 16.2 Hz, 1H), 6.89−6.94 (m, 2H), 7.45−7.52 (m, 3H); MS (pos. ESI): m/z = 177 (M^+); mp. 73−75 °C, lit.[50] mp.74−76 °C.

Batch Microwave Synthesis: Wittig Reaction (Table 3). To a solution of (acetylmethylene)triphenylphosphorane (**5**, 0.61 mmol, 195 mg, 1.7 equiv) in 3 mL of DMF, 44 μL of *p*-anisaldehyde (**4b**, 0.36 mmol) were added and the mixture was stirred for 30 s in a 10 mL Pyrex vial. The solution was capped with a Teflon septum and heated by microwave irradiation at 210 °C for 10 min. After cooling the vessel to ambient conditions, the crude reaction mixture was concentrated under reduced pressure and transferred to a silica-samplet, dried for 1 h at 50 °C in a drying oven and subjected to automated flash chromatography with petroleum ether/ethyl acetate (0 to 45% gradient) as eluent to provide 60 mg (95%) of 4-(4-methoxyphenyl)-3-buten-2-one (**1b**) in all respects identical to a sample prepared above.

Batch Microwave Synthesis: Aldol Condensation (Table 5). To a solution of *p*-anisaldehyde (**4b**, 2.50 mmol, 304 μL) in 2 mL of acetone, were added 60 μL of NaOH 10% solution and 1 mL of distilled water, and the mixture was stirred for 30 s in a 10 mL Pyrex vial. The solution was capped with a Teflon septum and heated by microwave irradiation at 120 °C for 1 min. After cooling the vessel to ambient conditions, the crude reaction mixture was concentrated under reduced pressure and transferred to a silica-samplet, dried for 1 h at 50 °C in a drying oven and subjected to automated flash chromatography with petroleum ether/ethyl acetate (0 to 45% gradient) as eluent to

provide 414 mg (94%) of 4-(4-methoxyphenyl)-3-buten-2-one (**1b**) in all respects identical to a sample prepared above.

Continuous Flow Synthesis: Mizoroki–Heck Reaction. To a stirred mixture of 4-iodoanisole (**3b**, 1.43 mmol, 335 mg), methyl vinyl ketone (2.14 mmol, 174 μL, 1.5 equiv), Cs_2CO_3 (1.57 mmol, 512 mg, 1.1 equiv) and DMF/H_2O (3:1) (5 mL) was added 5 mL of a 0.0008 M stock solution of $Pd(OAc)_2$ in DMF/H_2O (3:1) (0.64 mg, 0.2 mol %) and stirred for 30 s. At the same time the X-Cube Flash reactor was equipped with a stainless steel reaction coil (16 mL volume, 10 min residence time at 1.6 mL/min flow rate). The reaction parameters temperature (180 °C), pressure (60 bar) and 1.6 mL/min flow rate were selected on the flow reactor, and processing was started, whereby initially only solvent DMF/H_2O (3:1) was pumped through the system until the instrument had achieved the desired reaction parameters and stable processing was achieved. At that point the inlet tube was switched from the solvent flask to the 15-mL glass vial containing the reaction mixture. After processing through the flow reactor, the inlet flow was dipped back into the flask containing solvent and processed for an additional 10 min, thus washing from the system any remaining reaction mixture. Workup as above provided 169 mg (67%) of 4-(4-methoxyphenyl)-3-buten-2-one (**1b**) identical in all respects to a sample prepared above.

Continuous Flow Synthesis: Wittig Reaction. To a solution of (acetylmethylene)triphenylphosphorane (**5**, 2.04 mmol, 649 mg, 1.7 equiv) in 10 mL of DMF was added 135 μL of *p*-anisaldehyde (**4b**, 1.20 mmol), and the mixture was stirred for 30 s in a 15-mL Pyrex vial. At the same time the FlowSyn reactor was equipped with a stainless steel reaction coil (10 mL volume, 10 min residence time at 1 mL/min flow rate). The reaction parameters temperature (210 °C) and 1 mL/min flow rate were selected on the flow reactor, and processing was started, whereby initially only solvent DMF was pumped through the system until the instrument had achieved the desired reaction parameters and stable processing was achieved. At that point the inlet tube was switched from the solvent flask to the 15-mL glass vial containing the reaction mixture. After processing through the flow reactor, the inlet flow was dipped back into the flask containing solvent and processed for an additional 1 min, thus washing from the system any remaining reaction mixture. The reaction was concentrated under vacuum, and 205 mg (97%) of product **1b** was isolated as described above, identical in all respects with a sample prepared above.

Continuous Flow Synthesis: Aldol Reaction. To a solution of *p*-anisaldehyde (**4b**, 8.00 mmol, 972 μL) in 6.5 mL of acetone were added 192 μL of NaOH 10% solution and 3.5 mL of distilled water and stirred for 30s. At the same time the FlowSyn reactor was equipped with a stainless steel reaction coil (5 mL volume, 1 min residence time at 5 mL/min flow rate). The reaction parameters temperature (120 °C) and 5 mL/min flow rate were selected on the flow reactor, and processing was started, whereby initially only acetone solvent was pumped through the system until the instrument had achieved the desired reaction parameters and stable processing was achieved. At that point the inlet tube was switched from the solvent flask to the 15 mL glass vial containing the freshly prepared reaction mixture (a slow aldol condensation occurs also at room temperature). After processing through the flow reactor, the inlet flow was dipped back into the flask containing solvent and processed for an additional min, thus washing from the system any remaining reaction mixture. The reaction was concentrated under vacuum and 1.27 g (90%) of product **1b** was isolated as described above in all respects with a sample prepared above.

For dual feed processing the following procedure was used: a solution of *p*-anisaldehyde (**4b**, 8.00 mmol, 972 μL) in 6.5 mL of acetone [Reagent A] and a 0.14 M solution of NaOH (0.48 mmol) in H_2O (3.5 mL) [Reagent B] was prepared. At the same time the FlowSyn reactor was equipped with a stainless steel reaction coil (5 mL volume, 1 min residence time at 3.3 mL/min flow rate for Reagent A and 1.7 mL/min flow rate for Reagent B). The reaction parameters temperature (120 °C) and the different flow rates were selected on the flow reactor, and processing was started, whereby initially only pure solvents (acetone and water) were pumped through the system (ratio 2:1) until the instrument had achieved the desired reaction parameters and stable processing was achieved. At that point the inlet tubes from the pumps A and B were switched from the solvent flask to the corresponding glass vials containing the freshly prepared Reagent A and Reagent B. After processing through the flow reactor, the inlets were switched back to the flasks containing pure solvents and processing continued for an additional min, thus washing from the system any remaining reaction mixture. The reaction was concentrated under vacuum and 1.23 g (87%) of product **1b** were isolated as described above identical in all respects with a sample prepared above.

Continuous Mesofluidic Flow Synthesis: Aldol Reaction (Figure 1). The flow rate was set to 40 g/min (~45 mL/min). The starting solution was prepared from *p*-anisaldehyde (**4b**, 486 mL, 4.0 mol, 4.47 g/min, 0.033 mol/min) and NaOH (96 mL 10% aqueous solution, 0.2 mol, 0.09 g/min, 0.002 mol/min) in 3.25 L acetone (21.08 g/min, 0.36 mol/min) and 1.75 L deionized water (14.37 g/min). With pure acetone the pressure maintaining valve was adjusted to 7 bar. Together with 2 bar pressure drop from the residence time tubing an overall pressure of 9 bar was achieved. The silicon oil bath was heated to 120 °C. The process was started by feeding the starting solution into the system and putting the residence time tubing into the preheated silicon oil bath. A total volume of 4.65 L of output stream was collected. Two 100 mL samples were collected after 3 and 5.5 min from process start. Then four larger samples (~1.1 L) were collected in about 25 min each (after 8, 33, 58, and 82 min).

All samples have been analyzed as mentioned previously via HPLC and showed full conversion and the same selectivity as achieved in the small-scale experiments. A 1.1 L fraction was worked up. The solvent was evaporated, and the obtained precipitate was washed with a total volume of 1 L of distilled water and subsequently dried in a desiccator under vacuum to give the 4-(4-methoxyphenyl)but-3-en-2-one (**1b**) in almost quantitative yield.

4-(4-Methoxyphenyl)-butan-2-one (2b). *Continuous Flow Processing of Pure Substrate.* A 10 mL stock solution of 4-(4-methoxyphenyl)-3-buten-2-one (**1b**) with a 0.5 M concentration in EtOH was prepared in a glass vial. The reaction parameters (Full-H_2 mode, room temperature and 1.5 mL/min flow rate) were selected on the H-Cube hydrogenator. The instrument was fitted with a 30 mm Ra/Ni CatCart and the processing was started, whereby initially only pure solvent was pumped through the system until the instrument had achieved the desired reaction parameters and stable processing was achieved. At that point the sample inlet line was switched to the vial containing the substrate. A total reaction volume of 15 mL was collected and the cartridge subsequently washed with pure solvent for 5 min to remove any substrate/product

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still adsorbed on the catalyst. Evaporation of the solvent afforded 4-(4-methoxyphenyl)-butan-2-one (**2b**) as a yellow oil (97% crude yield), which was purified by flash chromatography to provide 838 mg of a pale-yellow oil (94%). ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.13 (s, 3H), 2.70−2.75 (m, 2H), 2.81−2.87 (m, 2H), 3.78 (s, 3H), 6.81−6.84 (m, 2H), 7.08−7.11 (m, 2H); MS (pos. ESI): m/z = 179 (M^+).

Via Two-Step Aldol/Hydrogenation Flow Sequence. To a solution of *p*-anisaldehyde (**4b**, 8.00 mmol, 972 μL) in 6.5 mL of acetone were added 192 μL of NaOH 10% solution and 3.5 mL of distilled water and stirred for 30 s. At the same time the FlowSyn reactor was equipped with a stainless steel reaction coil (5 mL volume, 1 min residence time at 5 mL/min flow rate). The reaction parameters temperature (120 °C) and 5 mL/min flow rate were selected on the flow reactor, and processing was started, whereby initially only acetone/water (2:1) as solvent was pumped through the system until the instrument had achieved the desired reaction parameters and stable processing was achieved. The reaction parameters for the selective double bond hydrogenation (Full-H_2 mode, 55 °C and 1 mL/min flow rate) were at the same time selected on the H-Cube hydrogenator. The instrument was fitted with a 30 mm Ra/Ni CatCart, and the processing was started, whereby initially only pure solvent was pumped through the system until the instrument had achieved the desired reaction parameters and stable processing was achieved. At that point the inlet line was switched to the vial containing the product from the aldol condensation step. A total reaction volume of 15 mL was collected and the cartridge subsequently washed with pure solvent for 5 min to remove any substrate/product still adsorbed on the catalyst. Evaporation of the solvent afforded 4-(4-methoxyphenyl)-butan-2-one (**2b**) as a yellow oil (93% crude yield), which was purified by flash chromatography to provide 1.07 g of a pale-yellow oil (75% over the two steps) identical in all respects with a sample prepared above.

4-(4-Hydroxyphenyl)-3-buten-2-one (1c). *Batch Microwave Synthesis: Mizoroki−Heck Reaction.* To 1 mL of DMF/H_2O (3:1) as solvent in a 10-mL Pyrex microwave vial were added 4-iodoanisole (**3c**, 0.43 mmol, 95 mg), methyl vinyl ketone (0.64 mmol, 52 μL, 1.5 equiv) and Cs_2CO_3 (0.47 mmol, 154 mg, 1.1 equiv), followed by 2 mL of 0.0004 M stock solution of $Pd(OAc)_2$ in DMF/H_2O (3:1) (0.19 mg, 0.2 mol %). The reaction mixture was stirred for 30 s, capped with a Teflon septum, and subjected to microwave heating for 20 min (hold time) at 160 °C. After cooling to ambient temperature, the crude reaction mixture was concentrated under reduced pressure and the residue subjected to automated flash chromatography with petroleum ether/ethyl acetate (0 to 45% gradient) as eluent to provide 54 mg (78%) of 4-(4-hydroxyphenyl)-3-buten-2-one (**1c**). ^{1}H NMR (300 MHz, $CDCl_3$): δ =2.38 (s, 3H), 6.09 (br s, 1H), 6.61 (d, J = 16.2 Hz, 1H), 6.91−6.86 (m, 2H), 7.52−7.43 (m, 3H); MS (pos. ESI): m/z = 163 (M^+); mp 111−113 °C, lit.[51] mp 111−112 °C.

Batch Microwave Synthesis: Wittig Reaction (Table 3). To a solution of (acetylmethylene)triphenylphosphorane (**5**, 0.61 mmol, 195 mg, 1.7 equiv) in 3 mL of DMF, was added 4-hydroxybenzaldehyde (**4c**, 44 mg,0.36 mmol), and the mixture was stirred for 30 s in a 10-mL Pyrex vial. The solution was capped with a Teflon septum and heated by microwave irradiation at 210 °C for 10 min. After cooling the vessel to ambient conditions, the crude reaction mixture was concentrated under reduced pressure and transferred to a silica-samplet, dried for 1 h at 50 °C in a drying oven, and subjected to automated flash chromatography with petroleum ether/ethyl acetate (0 to 45% gradient) as eluent to provide 41 mg (70%) of 4-(4-hydroxyphenyl)-3-buten-2-one (**1c**) in all respects identical to a sample prepared above.

Batch Microwave Synthesis: Aldol Condensation (Table 5). To a solution of 4-hydroxybenzaldehyde (**4c**, 2.50 mmol, 305 mg) in 2 mL of acetone was added 2 mL of a 10% aqueous NaOH solution, and the mixture was stirred for 30 s in a 10-mL Pyrex vial. The solution was capped with a Teflon septum and heated by microwave irradiation at 70 °C for 450 s. After cooling the vessel to ambient conditions, the crude reaction mixture was concentrated under reduced pressure and transferred to a silica-samplet, dried for 1 h at 50 °C in a drying oven, and subjected to automated flash chromatography with petroleum ether/ethyl acetate (0 to 45% gradient) as eluent to provide 280 mg (69%) of 4-(4-hydroxyphenyl)but-3-en-2-one (**1c**) identical in all respects to a sample prepared above.

Continuous Flow Synthesis: Wittig Reaction. To a solution of (acetylmethylene)triphenylphosphorane (**5**, 2.04 mmol, 649 mg, 1.7 equiv) in 10 mL of DMF was added 4-hydroxybenzaldehyde (**4c**, 146 mg,1.20 mmol), and the mixture was stirred for 30 s in a 15-mL Pyrex vial. At the same time the FlowSyn reactor was equipped with a stainless steel reaction coil (10 mL volume, 10 min residence time at 1 mL/min flow rate). The reaction parameters temperature (210 °C) and 1 mL/min flow rate were selected on the flow reactor, and processing was started, whereby initially only solvent DMF was pumped through the system until the instrument had achieved the desired reaction parameters and stable processing was achieved. At that point the inlet tube was switched from the solvent flask to the 15 mL glass vial containing the reaction mixture. After processing through the flow reactor, the inlet flow was dipped back into the flask containing solvent and processed for an additional 1 min, thus washing from the system any remaining reaction mixture. The reaction was concentrated under vacuum and 191 mg (98%) of product **1c** were isolated as described above, identical in all respects with a sample prepared above.

Continuous Flow Synthesis: Aldol Reaction. To a solution of 4-hydroxybenzaldehyde (**4c**, 6.25 mmol, 763 mg) in 5 mL of acetone was added 5 mL of a 10% aqueous NaOH solution, and the solution was stirred for 30 s. At the same time the FlowSyn reactor was equipped with a stainless steel reaction coil (10 mL volume, 450 s residence time at 1.34 mL/min flow rate). The reaction parameters temperature (70 °C) and 1.34 mL/min flow rate were selected on the flow reactor, and processing was started, whereby initially only solvent acetone was pumped through the system until the instrument had achieved the desired reaction parameters and stable processing was achieved. At that point the inlet tube was switched from the solvent flask to the 15 mL glass vial containing the freshly prepared reaction mixture (a slow aldol condensation occurs also at room temperature). After processing through the flow reactor, the inlet flow was dipped back into the flask containing solvent and processed for an additional 1 min, thus washing from the system any remaining reaction mixture. The reaction was concentrated under vacuum and 791 mg (78%) of product **1c** were isolated as described above, identical in all respects with a sample prepared above.

4-(4-Hydroxyphenyl)-butan-2-one (2c) (Table 7). A 10 mL stock solution of 4-(4-hydroxyphenyl)-3-buten-2-one (**1c**) with a 0.7 M concentration in DMF was prepared in a glass vial. The reaction parameters (Full-H_2 mode, 35 °C and 1 mL/min flow

rate) were selected on the H-Cube hydrogenator. The instrument was fitted with a 30 mm Ra/Ni CatCart and the processing was started, whereby initially only pure solvent was pumped through the system until the instrument had achieved the desired reaction parameters and stable processing was achieved. At that point the sample inlet line was switched to the vial containing the substrate. A total reaction volume of 15 mL was collected and the cartridge subsequently washed with pure solvent for 5 min to remove any substrate/product still adsorbed on the catalyst. Evaporation of the solvent affords 4-(4-hydroxyphenyl)-butan-2-one (**2c**) as a yellow oil (97% crude yield), which was purified by flash chromatography to provide 1.04 g of a pale yellow oil (91%).^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.14 (s, 3H), 2.70−2.75 (m, 2H), 2.80−2.86 (m, 2H), 4.86 (br s, 1H), 6.73−6.76 (m, 2H), 7.02−7.07 (m, 2H); MS (pos. ESI): m/z = 165 (M^+).

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