

Continuous Process for Phase-Transfer-Catalyzed Bisalkylation of Cyclopentadiene for the Synthesis of Spiro[2.4]hepta-4,6-diene

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Supporting Information

ABSTRACT: The transfer of a highly exothermic phase-transfer-catalyzed bisalkylation of cyclopentadiene with 1,2-dichloroethane from batch to continuous mode using standard and widely available laboratory equipment is presented. Besides the optimization of the reaction temperature and residence time, the efficient mixing of the organic phase (cyclopentadiene, 1,2-dichloroethane, and MeBu₃NCl) and the aqueous phase (30% NaOH) was studied in detail and optimized by the use of a simple, homemade “PTFE Raschig ring static mixer” consisting of a PTFE tube filled with small pieces cut from the same PTFE tube. A flow set-up with two PTFE Raschig ring static mixers and three residence time units with a three-stage temperature profile allowed the synthesis of highly energetic spiro[2.4]hepta-4,6-diene in a yield of 95% with a productivity of 15 g/h under safe conditions.

INTRODUCTION

Spiro[2.4]hepta-4,6-diene (**1**) is a key intermediate for the synthesis of an active pharmaceutical ingredient at Actelion Pharmaceuticals Ltd.¹ It can be prepared in semibatch mode by phase-transfer-catalyzed alkylation of cyclopentadiene with 1,2-dichloroethane using concentrated NaOH as the base at 50–60 °C.² A detailed thermal risk assessment of this reaction by Abele et al.³ points out the challenges of this synthesis: (a) cyclopentadiene is volatile (bp 39–43 °C) and unstable, with start of the decomposition reaction of –890 kJ/kg at approximately 60 °C;⁴ (b) the desired alkylation reaction itself is highly exothermic with a high maximum heat release rate (80–100 W/kg) and an inherent risk of accumulation if the addition of the reagents is done too fast or mixing is not efficient; and (c) the exothermic decomposition reaction of the final product **1** has a low onset temperature of 80 °C. This requires careful process control of the semibatch reaction and—if the purity is not sufficient for the subsequent reaction—distillation of **1**.

These challenges and the fact that we have to deal with a biphasic reaction motivated us to develop a flow process for the synthesis of **1**. Microreactors in the field of process chemistry often offer the exploration of “novel process windows”,⁵ hence their attractiveness. Better heat and mass transfers due to miniaturization and changing from classical “reaction time” known from classical batch reactions to “flow distance” in continuous reaction systems on the one hand enable the study of very short reaction times (so-called flash chemistry⁶) and on the other hand allow robust and efficient chemistry to be established. Flow chemistry also allows syntheses to be carried out at very high temperatures and pressures⁷ and opens up

possibilities to discover and exploit new chemical transformations.⁸

An important technical feature of this continuous reaction technology is the mixer. For very fast reactions (so-called type A, based on the classification by Roberge⁹), the right mixer design is crucial for a successful implementation of a continuous process. Another field where the mixing has a great impact on the process is the study of biphasic reactions, such as liquid/liquid¹⁰ or liquid/gas reactions,¹¹ hence mass-transfer-controlled reactions. Our interest is in liquid/liquid reactions, as we aimed for the transfer of an alkylation reaction of cyclopentadiene and 1,2-dichloroethane (organic phase) with aqueous NaOH as the base from batch mode to a continuous process. In microstructures, different flow patterns¹² for biphasic liquid/liquid mixtures can be observed depending on the type of mixer and flow rates: from annular or parallel flow, where the two immiscible liquids are just in contact via an interlayer, to slug flow, where large drops or segments of immiscible liquid are present in the liquid flow, to bubbly flow, where small droplets are dispersed in the flow (Figure 1).¹³ This bubbly flow is characterized by a high surface-to-volume ratio above 150 000 m² m⁻³. By coalescence, this bubbly flow goes back to slug flow with larger droplets. For phase-transfer-catalyzed reactions, one aims at either reproducible, small-segmented slug flow or, even better, bubbly flow to ensure efficient mixing and therefore fast reactions.¹⁴

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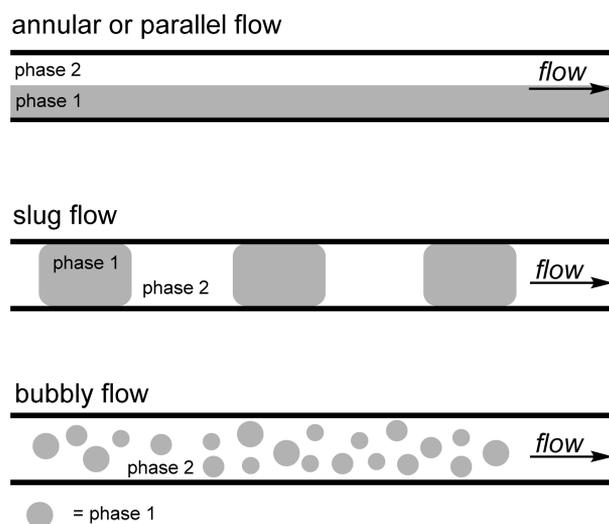


Figure 1. Schematic presentation of the different flow regimes.

Kobayashi¹⁵ reported a phase-transfer-catalyzed alkylation reaction of β -keto esters in microreactors and observed faster reaction using smaller channels (100 μm as opposed to 200/400 μm), resulting in “smaller/uniform” segmented flow. By careful optimization of the organic/aqueous phase ratio and the flow rate, Schouten and Hessel obtained uniform segmented slug flow and higher conversions and selectivities compared with the batch reaction for the phase-transfer-catalyzed alkylation of phenylacetonitrile.¹⁶ Working under bubbly-flow conditions, a redispersion (remixing) is needed to avoid coalescence and re-formation of slug flow. For example, Hessel and co-workers used a redispersion capillary to ensure bubbly flow within the whole capillary and therefore high and reproducible reaction rates for phase-transfer-catalyzed biphasic esterification.¹⁷ To ensure redispersion, Buchwald used a packed-bed reactor consisting of a tube filled with stainless steel beads (60–125 μm diameter) for biphasic C–N coupling reactions to give high and reproducible yields.¹⁸ Similarly, McQuade employed TEMPO-modified polymer beads in a catalytic packed-bed reactor as a remixing module for the biphasic bleach oxidation of alcohols.¹⁹

RESULTS AND DISCUSSION

First tests were performed in semibatch mode to evaluate the feasibility of transferring the reaction into a continuous process. We especially checked for the formation of any solids in the reaction mixture that might block the flow system. According to the published procedure,^{2,3} freshly prepared cyclopentadiene²⁰ was added to 8 equiv of 50% aqueous NaOH and 0.01 equiv of the phase-transfer catalyst (PTC) MeBu₃NCl, after which 1,2-dichloroethane was dosed over 2 h at 30 °C (Table 1). When the reaction was performed using Mettler EasyMax equipment, the exothermic reaction could be easily controlled by maintaining the ΔT between the temperature of the reaction mixture (T_r) and the temperature of the reactor jacket (T_j) at approximately 10 °C. Increasing the stirrer speed increased the reaction rate and ΔT accordingly. After the reaction, a dark-brown emulsion was obtained but no precipitate was observed! After aqueous workup and extraction of the product **1** with heptane, the yield was determined by NMR assay of the crude heptane solution with 1,4-dimethoxybenzene as an internal standard. When the mode of addition was changed by dosing of

Table 1. Semibatch synthesis of spiro[2.4]hepta-2,4-diene (**1**)

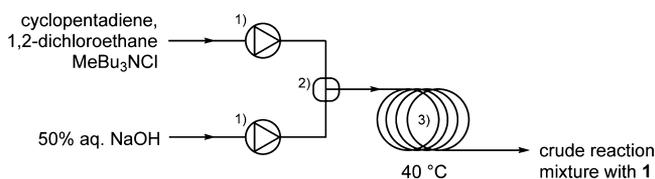
entry	conc. of NaOH (%)	yield (%)
1	50	59
2	50	78 ^a
3	40	63
4	30	63

^aNaOH was dosed over 1 h to a mixture of cyclopentadiene, 1,2-dichloroethane, and MeBu₃NCl.

50% aqueous NaOH solution over 1 h to a mixture of cyclopentadiene, 1,2-dichloroethane, and MeBu₃NCl (entry 2), the yield increased slightly from 59% to 78%. Again the exothermic reaction could be easily controlled (ΔT of $T_r/T_j \approx 10$ °C), and a second exotherm of approximately 15 min after addition was detected. During the reaction, no problems with precipitates were observed, nor were any byproducts such as vinyl chloride (by an elimination reaction of 1,2-dichloroethane) or dicyclopentadiene detected in the crude product by NMR analysis. Next, we evaluated the use of less concentrated aqueous NaOH solutions, keeping the 8 equiv constant (entry 3 and 4). The yields remained the same, but the advantage was that the reaction mixture was less viscous and the emulsion separated more slowly at higher temperature compared with the runs using 50% NaOH. Using less concentrated aqueous NaOH solution also has the benefit of better compatibility (less corrosive and less viscous) with the equipment such as pumps, tubing, and the glass microreactors.

On the basis of these initial results from the semibatch reaction, we designed a first flow system using an organic stream composed of a mixture of cyclopentadiene, 1,2-dichloroethane, and MeBu₃NCl, which was mixed with a stream of aqueous 50% NaOH solution at 40 °C in a microreactor followed by a residence time unit (Teflon tube). The reaction mixture was quenched at the exit of the flow reactor with ice–water, and after aqueous workup and extraction of **1** with heptane, the yield was determined by NMR assay of the neat heptane solution with 1,4-dimethoxybenzene as an internal standard.

The first continuous reactions were done using cyclopentadiene, 1 equiv of 1,2-dichloroethane, and 0.01 equiv of MeBu₃NCl as the organic stream and 8 equiv of 50% aqueous NaOH solution as the aqueous stream, keeping the reaction temperature constant at 40 °C. First we tested a simple T-mixer. At a residence time (t_R) of 10 min we got a yield of 25%, which was significantly lower than that of the semibatch reaction, but a clean and selective reaction was observed (Table 2, entry 1). Only the starting materials cyclopentadiene and 1,2-dichloroethane could be determined (by NMR) in the crude reaction mixture besides the desired product **1**. Similar to the batch reaction, no byproducts such as vinyl chloride or dicyclopentadiene were observed. The reaction mixture showed the typical reddish-brown color of the sodium cyclopentadiene salt, and in the Teflon tube we clearly saw two separate phases, indicating slug flow. Increasing the temperature to 50 °C to speed up the reaction caused evaporation of the cyclopentadiene (bp 42 °C) and bubble formation and “pulsation” of the liquid phase. At a residence time of 30 min, the reaction

Table 2. Initial “simple” microreactor set-up^a

¹⁾ Pumps; ²⁾ Mixer; ³⁾ Residence time unit (Teflon tubing)

entry	mixer type	t_R (min)	yield (%)
1	T-mixer	10	25
2	T-mixer	10	32 ^b
3	T-mixer	30	— ^c
4	LTF-MX	5	8
5	LTF-MX	10	32
6	LTF-MX	20	49
7	LTF-MX	20	56 ^b
8	LTF-MX	30	— ^c
9	Ehrfeld LH2	10	11

^aConditions: 1.0 equiv of 1,2-dichloroethane, 0.01 equiv of MeBu₃NCl, 8 equiv of 50% aq. NaOH, 40 °C; see the Experimental Section for more details on the set-up of the flow reactor system. ^bThe residence time unit was placed in an ultrasonic bath. ^cThe flow system was blocked, and no product could be isolated.

mixture became very viscous and precipitates formed at the interphases, which caused blocking of the system (entry 3). With an MX mixer, a split-and-combine mixer made from glass by Little Things Factory (LTF), better mixing of the biphasic reaction mixture was observed: the slug flow in the tube showed smaller segments, and at a residence time of 10 min the yield was slightly improved compared with the simple T-mixer (entry 5). At a residence time of 5 min (entry 4) the yield dropped drastically (to 8%), but at 20 min (entry 6) a reasonable yield of 49% was achieved, comparable to that of the semibatch reaction at 30 °C with an exothermic postreaction of approximately 15 min.

When the residence time was increased to 30 min, the system again became blocked as a result of the very viscous reaction mixture (Table 2, entry 8). The yield could be slightly increased by applying ultrasonication (entries 2 and 7),^{14c} but the effect was not significant (the accuracy of the NMR assays is approximately 1–2% for standard NMR²¹).

When an LH2 multilamination mixer from Ehrfeld was used (Table 2, entry 9), the yield of the spiro compound **1** was only about half of the yield obtained with the simple T-mixer. This was an astonishing result, but checking the data sheet of the LH2 mixer showed that we would need at least 10 times higher flow rates to have the appropriate energy input to obtain good mixing (≥ 15 mL/min compared with 1 mL/min as in our case). We also tried a redispersion capillary as described by Hessel.¹⁷ We modified a Teflon tube (i.d. = 2.8 mm, length = 90 mm) with inserts of small pieces of Teflon tube (o.d. = 2.8 mm, i.d. = 1.2 mm, length = 3 mm, distance between inserts = 5 mm; for more details see Supporting Information), but we could not observe any improvement in mixing or yield because the flow was too slow to create remixing (result not shown).

Next, we evaluated the influence of the concentration of the aqueous NaOH, the amount of the PTC, and the residence time (Table 3; microreactor set-up as in Table 2). A 10-fold increase in the amount of the PTC at a residence time of 10 min blocked the flow system: the reaction mixture immediately

Table 3. Variation of the NaOH concentration, PTC loading, and residence time with the initial flow reactor set-up^a

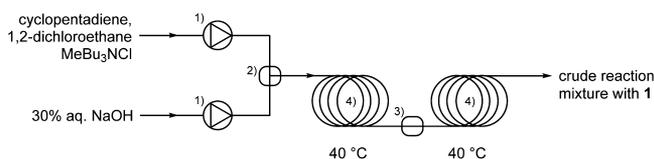
entry	mixer	equiv of PTC	conc. of NaOH (%)	t_R (min)	yield (%)
1	LTF-MX	0.01	50	10	31
2	LTF-MX	0.1	50	5	32
3	LTF-MX	0.1	50	10	— ^b
4	LTF-MX	0.1	30	10	43
5	LTF-MX	0.1	30	20	49
6	LTF-MX	0.05	30	30	46

^aConditions: 1.0 equiv of 1,2-dichloroethane, 8 equiv of NaOH, 40 °C; microreactor set-up as in Table 2. ^bThe flow system was blocked, and no product could be isolated.

turned dark brown, and by the end of the residence time unit the Teflon tube was blocked completely (entry 3). When the residence time was shortened to 5 min (entry 2), the reaction mixture remained “liquid” at the exit of the tube and the yield was 32%, nearly quadruple that with 0.01 equiv of PTC (8% yield; see Table 2, entry 4).

To avoid the blocking of the microreactor system by the increased viscosity of the reaction mixture and/or formation of solids, we changed to a more dilute 30% aqueous NaOH solution. The 8 equiv of base was kept constant, which was adjusted by the flow ratio of the pumps. The aspect of the reaction mixture at the exit of the reactor was right away more “liquid”, and residence times of 20 or even 30 min were possible without blocking of the tubes (Table 3, entries 5 and 6). In all of the tests, the yield did not exceed 50%: even with 0.1 equiv of MeBu₃NCl and a prolonged residence time, starting material (cyclopentadiene and 1,2-dichloroethane) remained in the crude product mixture. Small bubbles were clearly discerned, indicating good mixing of the biphasic reaction mixture after the LTF-MX mixer, but thereafter this bubbly flow coalesced and turned into slug flow in the residence time unit (as judged by visual inspection). This observation prompted us to study a multi-mixer set-up that forces this slug flow to remix again.

This new set-up featured a second mixer between two residence time units (see Table 4). At a residence time of 10 min, this new set-up resulted in an increase in the yield by 10% (entries 5 and 6), and at a residence time of 20 min the yield increased by 5% (entries 7 and 8). The remixing had a beneficial effect, but optical examination revealed that the organic and aqueous phases remained segmented after the additional LTF-MX mixer. To see whether an increased flow rate at the same residence time would give better mixing, we doubled the reactor volume from 10 to 20 mL by doubling the length of the residence time unit and adjusted the flow rate by a factor of 2 to keep the residence time constant (entry 3). Obviously, this higher energy input by the pumps had no significant impact on the yield (Figure 2). The graph in Figure 2 clearly illustrates that even with increased residence times the yield stalled at approximately 50%. One can also see that the new set-up with an additional mixer increased the yield (compared with the data for the set-up with just one mixer, indicated by ■). In order to improve the yield, the mixing efficiency of the flow system had to be optimized. Increasing the temperature to drive the reaction to completion was not feasible, as at reaction temperatures above 80 °C the product **1** starts to decompose violently.³

Table 4. Test of a multi-mixer set-up^a

1) Pumps; 2) Mixer *i*; 3) Mixer *ii*; 4) Residence time unit (Teflon tubing)

entry	mixer type		t_R (min)	yield (%)
	mixer <i>i</i>	mixer <i>ii</i>		
1	LTF-MS	LTF-MX	0.5	20
2	LTF-MS	LTF-MX	2	35
3	LTF-MS	LTF-MX	2	34 ^b
4	LTF-MS	LTF-MX	5	49
5	LTF-MX	–	10	43
6	LTF-MS	LTF-MX	10	53
7	LTF-MS	–	20	49
8	LTF-MS	LTF-MX	20	54

^aConditions: 1.0 equiv of 1,2-dichloroethane, 0.1 equiv of MeBu₃NCl, 8 equiv of 30% NaOH, 40 °C. ^bThe reactor volume and flow rate were doubled.

In the set-up in Table 4, we could observe good mixing in the beginning, as just after the first LTF-MS mixer we had bubbly flow. However, after a few centimeters the two phases started to separate in the Teflon tube, and we observed slug flow with less contact between the phases, thus limiting the reaction rate. To overcome the coalescence of the two immiscible phases either remixing as described by Hessel¹⁷ or a packed-bed reactor as described by Buchwald¹⁸ and McQuade¹⁹ are conceivable options. In addition, some bubbles were observed, most probably due to evaporation of cyclopentadiene. Therefore, a staggered temperature profile was deemed ideal to cope with this evaporation and with the challenge of decomposition at prolonged exposure to high temperature and stalled conversion.

The next flow reactor set-up (see Table 5) entailed a series of mixers at the start (a LTF-MX mixer, an LTF-VS residence

time unit with an integrated snake mixer unit, and finally an additional LTF-MX mixer as a remix unit) followed by three residence time units held at increasing temperatures. The second mixer was placed before the last residence time unit (Table 5). Already in the first run the yield of **1** increased to 75% (entry 1), and by visual examination one could easily observe much better mixing right after the first series of mixers and “smaller” segmentation of the two phases in the Teflon tube coils. The yield increased by 10% when the amounts of both the PTC and 1,2-dichloroethane were increased (entry 2). This improved yield of 85% was maintained also with an enlarged reactor volume (PTFE tubing with i.d. = 2.4 mm instead of 1 mm) and flow rates (both by a factor of 3) while the residence time was kept constant at 25 min (entry 3). Compared with all of the proceeding tests (Tables 2–4), no traces of the cyclopentadiene starting material were detected in the crude product.

Corrosion of the LTF glass reactors and the aluminum case led to breaking of the glass flow reactors. These problems prompted us to develop our own “PTFE Raschig ring static mixer” (RRSM) inspired by the packed-bed reactors of Buchwald¹⁸ and by McQuade.¹⁹ This was done by filling a Teflon tube (i.d. = 2.4 mm, length = 50 cm) with self-made Raschig rings made by cutting a Teflon tube (o.d. = 1.6 mm, i.d. = 1.0 mm) perpendicular to the axis of the tube into small pieces with lengths of 1–2 mm. This self-made RRSM was integrated into the set-up of Table 5 by using a T-mixer connected to the two exits of the pumps instead of the LTF-MX/VS/MX mixer sequence. The yield for this new mixer set-up was 80% and in a run over 7 h even 85% (entries 4 and 5). Very efficient mixing resembling bubbly flow was observed at the exit of the RRSM, which then coalesced back to segmented flow in the residence time units. With an additional self-made RRSM as a remixing unit (mixer *ii*), the yield of **1** even increased to 95%. Operating the flow reactor for 1.3 h, we produced 19.8 g of **1** as a solution in heptane (10.5% w/w by NMR assay). The productivity for this final set-up was 14.8 g of **1**/h (entry 6). The only impurities detected by ¹H NMR

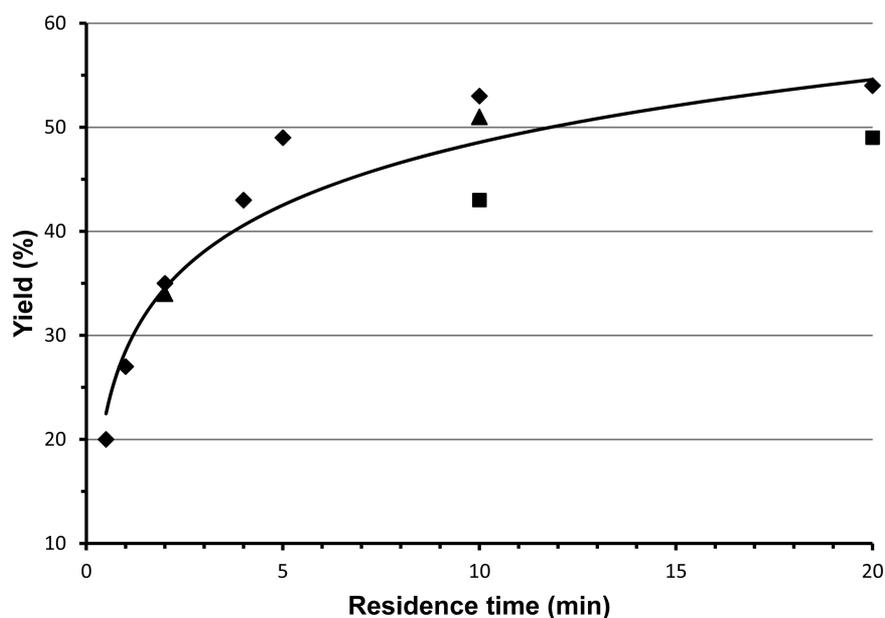
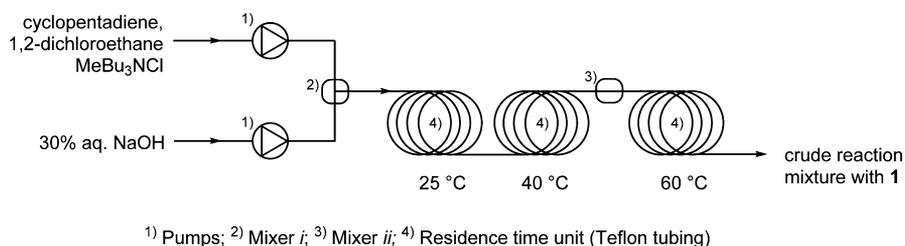


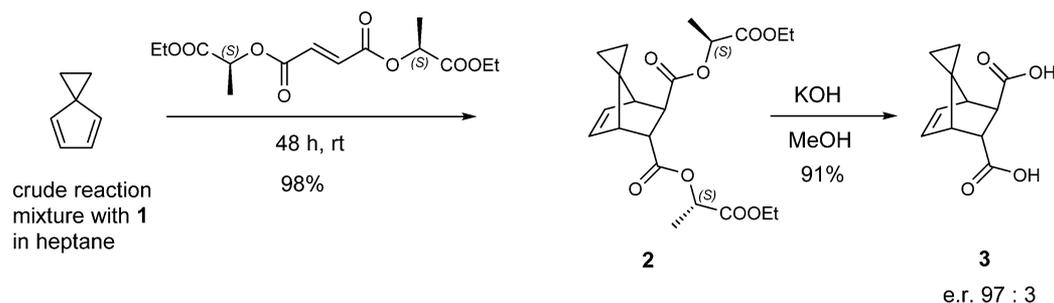
Figure 2. Yield of **1** as a function of the residence time. Values from Table 4: ◆, set-up with two mixers; ▲, set-up with two mixers at the same t_R but double the flow rate; ■, set-up with one mixer.

Table 5. Optimization of the multi-mixer set-up and the amounts of PTC (MeBu₃NCl) and 1,2-dichloroethane (DCE)

entry	mixer type		equiv of PTC	equiv of DCE	t_R (min)	yield (%)
	mixer <i>i</i>	mixer <i>ii</i>				
1	LTF-MX/VS/MX	LTF-MX	0.12	1	20	75
2	LTF-MX/VS/MX	LTF-MX	0.14	1.2	20	85
3	LTF-MX/VS/MX	LTF-MX	0.14	1.4	25	85
4	T-mixer/RRSM ^a	–	0.14	1.4	25	80
5	T-mixer/RRSM ^a	–	0.14	1.4	25	85 ^b
6	T-mixer/RRSM ^a	RRSM ^a	0.14	1.4	25	95 ^c

^aSelf-made “PTFE Raschig ring static mixer” (RRSM). ^bProduction run over 7 h. ^c19.8 g of **1** was produced in 1.3 h.

Scheme 1. Subsequent Diels–Alder reaction of **1**



analysis were 1,2-dichloroethane and traces of dicyclopentadiene. Attempts to purify **1** by distillation from the crude reaction mixture were not successful because of the similarity of the boiling points of **1** and heptane. Instead, the crude product **1** was sufficiently pure to be used directly in the subsequent Diels–Alder reaction, as shown in Scheme 1. The Diels–Alder product **2** was formed in 98% yield with a diastereomeric ratio of 94:6, which compares favorably with the results obtained using **1** purified by distillation (78% yield).^{1,3,22} Saponification of the Diels–Alder adduct **2** yielded the dicarboxylic acid **3** in 91% yield as a crystalline material, and an enantiomeric ratio (e.r.) of 97:3 was determined by HPLC.

The results obtained from the optimized flow reactor synthesis (Table 5, entry 6) were compared with the data for the batch reaction (Table 1, entry 2), as shown in Table 6. A major difference was the larger excess of 1,2-dichloroethane and greater amount of MeBu₃NCl used in the flow synthesis. These two parameters were decisive in reaching complete conversion and therefore a high yield of **1** in the continuous process. It is important to note that using larger amounts of these two reagents, MeBu₃NCl and 1,2-dichloroethane, had no detrimental impact on the quality of the final Diels–Alder product. The use of a less concentrated aqueous NaOH solution was based just on practical reasons: a less viscous reaction mixture and less corrosion at similar reactivity were achieved. The yields and purities of **1** are comparable or even better for the flow reaction than for the batch reaction. This was confirmed by the subsequent Diels–Alder reaction (Scheme 1). When distilled **1** originating from a batch reaction was used, the overall yield and

Table 6. Comparison of the batch and flow modes

	batch reaction ^a	flow reaction ^b
cyclopentadiene/1,2-dichloroethane/MeBu ₃ NCl molar ratio	1:1:0.01	1:1.4:0.14
conc. of NaOH ^c	50%	30%
reaction temperature	30 °C	25 °C/40 °C/60 °C
residence time	– ^d	25 min
yield	78%	95%
purity (by NMR assay)	95% w/w	95% w/w
productivity of 1	–	14.8 g/h

^aData from the reaction in Table 1, entry 2. ^bData from the reaction in Table 5, entry 6. ^c8 equiv for the batch and flow reactions. ^dDosing over 1 h, postreaction 30 min.

e.r. of the dicarboxylic acid **3** was similar. The productivity of 15 g/h should be easily increased by the use of a larger flow system, provided that the mixing is similarly efficient (for a discussion of the scale-up of continuous processes, see refs 10a and 23).

CONCLUSION

The semibatch biphasic synthesis of spiro[2.4]hepta-4,6-diene (**1**) was successfully transferred into a high-yielding continuous process. A key feature of the new process is a specifically designed mixer to secure the desired flow regime within the flow system. The careful choice of the concentration of the aqueous NaOH solution and the adjusted amounts of 1,2-dichloroethane and MeBu₃NCl as the phase-transfer catalyst

allowed a practical residence time of 25 min for complete conversion. A well-adapted temperature profile of three residence time units was required in order to reconcile the constraints imposed by the boiling point of cyclopentadiene and the increasing viscosity of the reaction mixture while maximizing the conversion. By optimization of the reactor design, the temperature ramp, and the reaction conditions, the yield of **1** was improved from 32% using a simple T-mixer to approximately 50% using two LTF-MX glass mixers and finally to 95% using new, simple, and cheap "Raschig ring static mixers" (RRSMs). Our self-made RRSMs were made from simple Teflon tubing and proved to be efficient mixers for biphasic and corrosive media. These RRSMs can be simply adapted in their design (i.d., length) and materials (e.g., glass or stainless steel) to any flow chemistry problem. Additional work is currently ongoing for the characterization of the RRSM in terms of pressure drop, mixing characteristics, and flow regime of the mixer, residence time distribution, "scalability" of the RRSM, and prolonged use.

EXPERIMENTAL SECTION

General. The chemicals were reagent grade and used as supplied, unless stated otherwise. The cracking of dicyclopentadiene into cyclopentadiene was done at 160 °C (IT), and the freshly distilled cyclopentadiene (bp 42 °C) was collected and stored at -20 °C.²⁰

¹H (300 MHz) and ¹³C NMR (75 MHz) spectra were recorded on a Bruker AVANCE 300 spectrometer. Chemical shifts (δ) are reported in parts per million relative to Me₄Si (0.00 ppm). The contents (% w/w) of all crude products and reaction mixtures were assessed by NMR assay with 1,4-dimethoxybenzene as an internal standard. For **1**, integrals of the signals of the cyclopentadiene hydrogens (two multiplets at 6.1 and 6.5 ppm) were compared to the integral of the methyl singlet of 1,4-dimethoxybenzene (at 3.56 ppm). In all cases, the time between scans (the relaxation delay, D1) was set to 20 s.

Flow Reactor Set-Up. The T-mixer was purchased from Bola (Germany); the LTF-MX (volume = 0.2 mL, channel size = 1 mm), LFT-MS (volume = 0.2 mL, channel size = 1 mm), and LTF-VS (volume = 1.1 mL, channel size = 1 mm) were purchased from Little Things Factory (www.ltf-gmbh.com). The residence time units were prepared from Teflon tubing. For heating, the reactors were immersed in a water bath. The feed was pumped using an NE-1010 syringe pump from New Era Pump Systems Inc. (www.syringepump.com).

Syntheses of Spiro[2.4]hepta-4,6-diene (1). *Semibatch Synthesis* (Table 1, Entry 2). A reactor was charged with freshly prepared cyclopentadiene (9.0 g, 7.2 mL, 136.2 mmol, 1 equiv), MeBu₃NCl (320 mg, 1.36 mmol, 0.01 equiv), 2,6-di-*tert*-butyl-4-methylphenol (BHT) (20 mg, 0.1 mmol), and 1,2-dichloroethane (13.5 g, 16.7 mL, 136.2 mmol, 1 equiv). The temperature was set to 30 °C and the stirrer speed to 500 rpm. To the clear solution was dosed 50% aqueous NaOH solution (88.0 g, 58 mL, 1.1 mol, 8 equiv) over 1 h. During the addition, the reaction mixture became dark brown and viscous. After an additional 30 min, the reaction mixture was cooled to 10 °C and diluted with H₂O (60 mL) while the temperature rose to 23 °C. The dark-brown emulsion was diluted with heptane (90 mL), and the phases were separated. The organic layer was washed twice with H₂O (40 mL), once with 1 M HCl solution (40 mL), and twice with H₂O (40 mL). The organic layer was dried over MgSO₄ and filtered, and **1** was obtained as a solution in heptane (88.7 g). By ¹H NMR assay with 1,4-

dimethoxybenzene, this solution contained 11% w/w **1**, corresponding to a yield of 78%. The analytical data correspond to the literature data.²

¹H NMR (CDCl₃): δ 1.67 (s, 4H, cyclopropyl); 6.1–6.15 (m, 2H, CH); 6.5–6.6 (m, 2H, CH).

"Simple" Flow Reactor (Table 2, Entry 6). The flow reactor consisted of an LTF-MX mixer (0.2 mL) and coiled Teflon tube (20 mL, length = 1050 cm, i.d. = 1.56 mm), which was kept at 40 °C (Configuration shown in Table 2). Feed 1 (6.05 mmol of cyclopentadiene/mL) was prepared by mixing cyclopentadiene (16.0 g, 20 mL, 242 mmol, 1 equiv), 1,2-dichloroethane (24.0 g, 19.4 mL, 242 mmol, 1 equiv), BHT (30 mg), and MeBu₃NCl (570 mg, 2.4 mmol, 0.01 equiv) and was pumped at a flow rate of 0.355 mL/min. Feed 2 consisted of 50% aqueous NaOH solution and was pumped at a flow rate of 0.645 mL/min. The total flow rate was 1.0 mL/min, corresponding to a residence time of 20 min. The reactor was run under these conditions for 35 min before the reaction mixture was collected during 22 min (theoretical yield of **1**: 47.3 mmol) by quenching into H₂O (150 mL) at 0 °C. The dark-brown emulsion was diluted with heptane (50 mL), and the phases were separated. The organic layer was washed twice with H₂O (40 mL), once with 1 M HCl solution (40 mL), and twice with H₂O (40 mL). The organic layer was dried over MgSO₄ and filtered, and **1** was obtained as a solution in heptane (27.0 g). This solution contained 8% w/w **1** as determined by ¹H NMR assay, corresponding to a yield of 49%.

"Multi-Mixer" Flow Reactor (Table 4, Entry 8). The flow reactor consisted of an LTF-MS mixer (0.2 mL), a coiled Teflon tube (9.8 mL, length = 1250 cm, i.d. = 1.0 mm), an additional LTF-MX mixer (0.2 mL), and an additional coiled Teflon tube (9.8 mL, length = 1250 cm, i.d. = 1.0 mm). The total volume was 20 mL, and the set-up was kept at 40 °C (the configuration is shown in Table 4). Feed 1 (5.35 mmol of cyclopentadiene/mL) was prepared by mixing cyclopentadiene (7.1 g, 8.9 mL, 107 mmol, 1 equiv), 1,2-dichloroethane (10.6 g, 8.6 mL, 107 mmol, 1 equiv), BHT (20 mg), and MeBu₃NCl (2.54 g, 10.7 mmol, 0.1 equiv) and was pumped at a flow rate of 0.188 mL/min. Feed 2 consisted of 30% aqueous NaOH solution and was pumped at a flow rate of 0.812 mL/min. The total flow rate was 1.0 mL/min, corresponding to a residence time of 20 min. The reactor was run under these conditions for 35 min before the reaction mixture was collected during 43 min (theoretical yield of **1**: 43.2 mmol) by quenching into H₂O (150 mL) at 0 °C. The dark-brown emulsion was diluted with heptane (50 mL), and the phases were separated. The organic layer was washed twice with H₂O (50 mL), once with 1 M HCl solution (50 mL), and twice with H₂O (50 mL). The organic layer was dried over MgSO₄ and filtered, and **1** was obtained as a solution in heptane (43.3 g). This solution contained 5% w/w **1** as determined by ¹H NMR assay, corresponding to a yield of 54%.

"RRSM" Flow Reactor (Table 5, Entry 6). The flow reactor consisted of a T-mixer, an RRSM (1.5 mL, length = 50 cm, i.d. = 2.4 mm), a coiled Teflon tube (18 mL, length = 400 cm, i.d. = 2.4 mm) kept at 25 °C, an additional coiled Teflon tube (18 mL, length = 400 cm, i.d. = 2.4 mm) kept at 40 °C, a second RRSM (1.5 mL, length = 50 cm, i.d. = 2.4 mm), and an additional coiled Teflon tube (36 mL, length = 800 cm, i.d. = 2.4 mm) kept at 60 °C. The total volume was 75 mL (the configuration is shown in Table 5). Feed 1 (4.4 mmol of cyclopentadiene/mL) was prepared by mixing cyclopentadiene (29.0 g, 36.3 mL, 439 mmol, 1 equiv), 1,2-dichloroethane (60.8

g, 49.2 mL, 614 mmol, 1.4 equiv), and MeBu₃NCl (14.5 g, 61.5 mmol, 0.14 equiv) and was pumped at a flow rate of 0.663 mL/min. Feed 2 consisted of 30% aqueous NaOH solution and was pumped at a flow rate of 2.337 mL/min. The total flow rate was 3.0 mL/min, corresponding to a residence time of 25 min. The reactor was run under these conditions for 40 min before the reaction mixture was collected during 1 h 20 min (theoretical yield of **1**: 232.5 mmol) by quenching into H₂O (100 mL) and heptane (200 mL) at 0 °C, which afforded a dark-brown emulsion. The phases were separated, and the organic layer was washed twice with H₂O (50 mL), once with 1 M HCl solution (50 mL), and twice with H₂O (50 mL). The organic layer was dried over MgSO₄ and filtered, and **1** was obtained as a yellowish solution in heptane (188.3 g). This solution contained 10.5% w/w **1** as determined by ¹H NMR assay, corresponding to a yield of 95%.

Synthesis of (1R,4S,5R,6R)-Bis((S)-1-ethoxy-1-oxopropan-2-yl) Spiro[bicyclo[2.2.1]hept-2-en-7,1'-cyclopropan]-5,6-dicarboxylate (2). To a solution of **1** in heptane (154.5 g, NMR assay 10.5% w/w, 176 mmol) was added (–)-bis[(S)-1-(ethoxycarbonyl)ethyl] fumarate (66.8 g, 211 mmol, 1.2 equiv) at rt. The mixture was stirred for 48 h at rt and then concentrated under reduced pressure to yield **2** (84.8 g, NMR assay 83% w/w, corresponding to an assay-corrected yield of 98%, d.r. 94:6) as a yellow oil. For analytical purposes, a 2.00 g sample of crude **2** was purified by column chromatography (EtOAc/heptane 15:85) to yield pure **2** (1.58 g, 79%) as a colorless oil. *R*_f 0.30 (EtOAc/heptane 15:85); ¹H NMR (300 MHz, CDCl₃) δ 0.36–0.58 (m, 3H), 0.60–0.76 (m, 1H), 1.27 (td, *J* = 7.1, 1.3 Hz, 6H), 1.49 (dd, *J* = 7.1, 4.6 Hz, 6H), 2.74–2.82 (m, 1H), 2.82–2.87 (m, 1H), 2.90 (d, *J* = 4.6 Hz, 1H), 3.74 (dd, *J* = 4.1, 4.3 Hz, 1H), 4.19 (qd, *J* = 7.1, 0.8 Hz, 3H), 4.13–4.25 (m, 1H), 5.07 (dq, *J* = 15.8, 7.1 Hz, 2H), 6.30 (ddd, *J* = 5.8, 2.8, 0.7 Hz, 1H), 6.42 (ddd, *J* = 5.8, 3.1, 0.7 Hz, 1H); ¹³C NMR (75 MHz, CDCl₃) δ 4.9, 8.5, 14.12, 14.14, 16.98, 16.99, 44.2, 47.2, 48.7, 51.9, 52.0, 61.25, 61.31, 68.6, 68.7, 135.4, 137.4, 170.7, 170.8, 172.5, 172.6; IR (neat) 1017, 1048, 1092, 1131, 1168, 1450, 1734, 2942, 2988, 3070 cm⁻¹; [α]_D²⁰ –105.7 (*c* 2.0, EtOH).

Synthesis of (1R,4S,5R,6R)-Spiro[bicyclo[2.2.1]hept-2-en-7,1'-cyclopropan]-5,6-dicarboxylic Acid (3). To a solution of crude **2** (82.8 g, NMR assay 83% w/w, 0.168 mol) in MeOH (250 mL) was added a 16% aqueous solution of NaOH (250 mL). The mixture was stirred for 30 min at 65 °C, whereupon the starting emulsion disappeared. Methanol was evaporated off, and the residue was diluted with water (150 mL). The mixture was treated with charcoal and filtered through HyFlo. The product was precipitated by the addition of 32% HCl (135 mL). The suspension was cooled to 5 °C, filtered, washed with cold water, and dried under vacuum to yield **3** (31.7 g, 91%) as a white crystalline solid. *R*_f 0.30 (EtOAc/heptane 1:1); mp 161–163 °C; ¹H NMR (300 MHz, DMSO-*d*₆) δ 1.30–1.39 (m, 2H), 0.40–0.52 (m, 2H), 2.54–2.64 (m, 3H), 3.42 (t, *J* = 4.2 Hz, 1H), 6.11 (dd, *J* = 5.5, 2.6 Hz, 1H), 6.37 (dd, *J* = 5.5, 3.0 Hz, 1H), 12.23 (s, 2H); ¹³C NMR (75 MHz, DMSO-*d*₆) δ 4.7, 8.2, 44.2, 47.5, 48.4, 50.5, 50.6, 134.7, 137.6, 174.10, 174.12; IR (neat) 669, 695, 752, 1163, 1385, 1423, 1683, 1718, 2976, 3170 cm⁻¹; [α]_D²⁰ –64.4 (*c* 2.0, EtOH); HPLC (ChiralPak AD-H, 4.6 mm × 250 mm, 5 μm; heptane/EtOH 0.1% TFA 60:40; 0.8 mL min⁻¹; 25 °C; 210 nm) *t*_R(minor) 8.6 min, *t*_R(major) 9.9 min, e.r. = 97:3.

■ ASSOCIATED CONTENT

§ Supporting Information

¹H NMR spectra and pictures of flow reactors. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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Notes

The authors declare no competing financial interest.

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