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Investigation into an Unexpected Impurity: a Practical Approach to Process Development for the Addition of Grignard Reagents to Aldehydes Using Continuous Flow Synthesis

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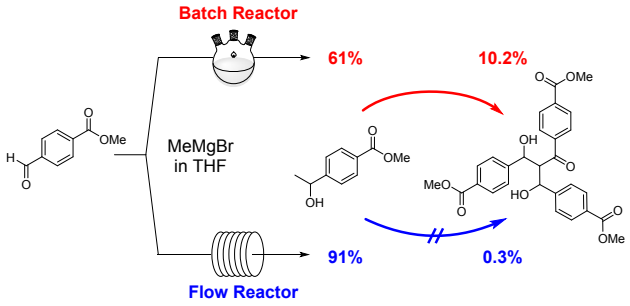
TOC



ABSTRACT

This work presents a case study of process development using continuous flow synthesis. In developing a process for manufacturing drug substances in batch reactors, we unexpectedly obtained a significant amount of a trimerized byproduct on addition of MeMgBr to an aldehyde. Consideration of a plausible generation mechanism for the byproduct indicated that it arose from a reaction between the starting material and the Mg salt of the target product. This led us to try applying continuous flow synthesis to the process to shorten the time during which the starting material coexists with the Mg salt of the target product. This led to drastic suppression of the byproduct under very mild conditions and the establishment of a more robust process than that for batch reactors.

KEYWORDS: *process development, Grignard reagent, aromatic aldehyde, trimerized byproduct, continuous flow synthesis, fast mixing*

INTRODUCTION

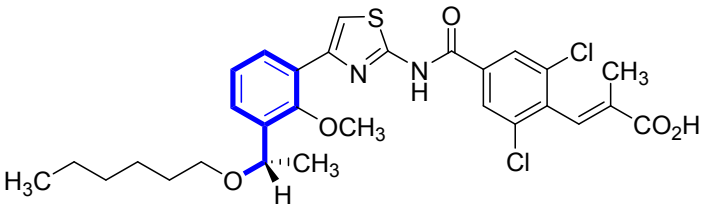
This work suggests a practical approach using continuous flow synthesis, which was established during process development for the addition of Grignard reagents.

Grignard reagents offer a versatile synthetic strategy to construct C–C bonds.[1] In contrast with organic lithium reagents, which work in a similar manner,[2] Grignard reagents can generally be stored at room temperature whereas organic lithium reagents often need to be stored at low temperature.[3] Also, while organic lithium reagents are used under cryogenic conditions, Grignard reagents are used at relatively mild temperatures without the need for excess cooling.[4] However,

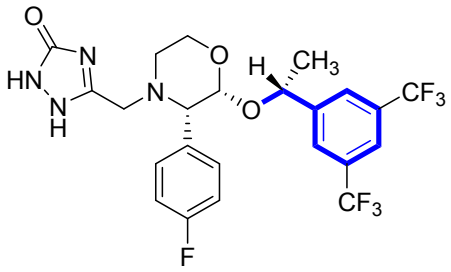
establishing a high yield with a Grignard reagent at room temperature is often still challenging. Pursuing milder reaction conditions on the application of Grignard reagents remains meaningful.

Although Grignard reagents are useful for constructing C–C bonds, the generation of Grignard reagents with halides and metal magnesium is a highly exothermic reaction and can be troublesome for a large-scale batch.[5] Knochel *et al.* reported a method for preparing a variety of organomagnesium reagents under mild conditions via metal-halogen exchange.[6] This methodology can facilitate preparation of highly functionalized Grignard reagents, which can be used to synthesize complex molecules, such as active pharmaceutical ingredients.

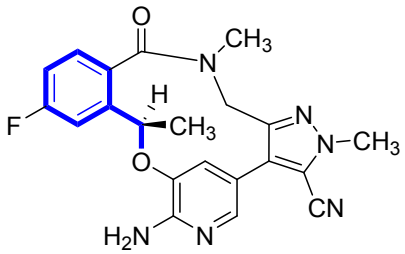
Addition of Grignard reagents to benzoyl moieties can provide important structural units of drug substances. As shown in Figure 1, lusutrombopag,[7] aprepitant[8] and lorlatinib[9] have this unit, and the development of this reaction procedure should greatly aid the manufacturing of drug substances.



lusutrombopag



aprepitant



lorlatinib

Figure 1. Structures of drug substances bearing a unit which can be constructed by addition of Grignard reagents to benzoyl moieties.

Recently, regulatory agencies have recommended the application of continuous manufacturing, including continuous flow synthesis, for pharmaceutical production.[10, 11] From the viewpoint of organic synthesis, continuous flow synthesis has three advantages[12]: 1) precise temperature control can be conducted easily due to high heat exchange efficiency; 2) fast mixing can be done using a micromixer; and 3) residence time can be strictly controlled by setting the flow rates and internal volumes of reactors. These advantages can help improve the quality of drug substances and the robustness of manufacturing processes. However, continuous manufacturing of drug substances with continuous flow synthesis has been limited despite the possible wide range of applications.[13] One of the issues is insufficient discussion about whether the effectiveness and robustness of continuous flow synthesis are actually superior to those of batch synthesis. Therefore, the applicability of continuous flow synthesis directed toward manufacturing drug substances needs to be examined on a regular basis.

Herein we report the generation of an unexpected byproduct during addition of MeMgBr to methyl 4-formyl benzoate during the development of a process for manufacturing drug substances. We found that this byproduct could be suppressed under very mild conditions using continuous flow synthesis.[14] We then examine the robustness of the continuous flow system and the generality of the application of this system for versatile substrates.

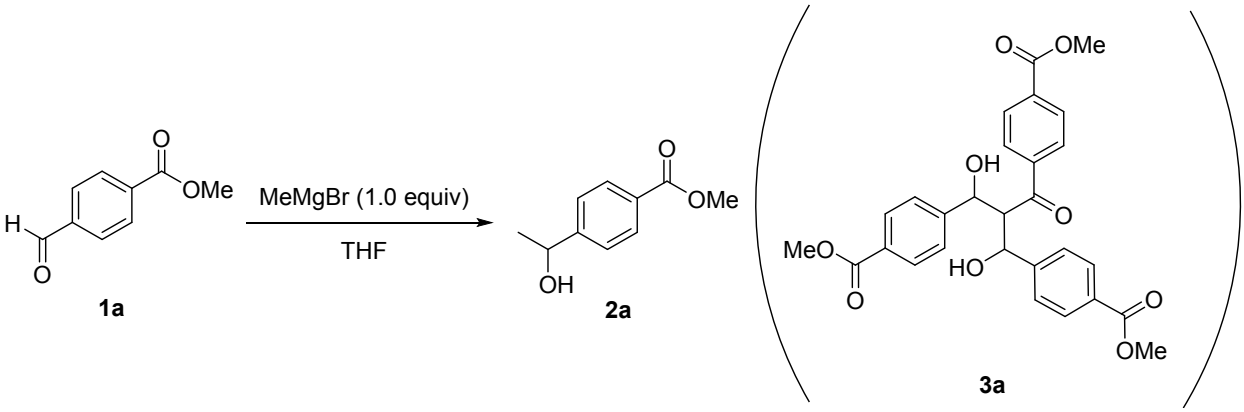
RESULTS AND DISCUSSION

In manufacturing drug substances, addition reaction of MeMgBr to methyl 4-formyl benzoate (**1a**) bearing an ester group, which can be converted to other functional groups, has been developed. During our development of the process for batch reactors, addition of a solution of MeMgBr in THF to a solution of **1a** in THF gave a significant amount of an unexpected byproduct **3a** (Scheme 1). Extensive investigation including ^{1}H NMR, ^{13}C NMR, 2D NMR (^{1}H-^{1}H COSY, ^{1}H-^{13}C HSQC, and ^{1}H-^{13}C HMBC), and mass spectroscopy of the isolated byproduct showed that it had a trimerized structure with the methyl ester group tolerated.[15] A plausible generation mechanism for the trimerized byproduct **3a** is shown in Scheme 1. During addition of MeMgBr, the starting material **1a** and the Mg salt of the target product **2a** coexist in the reaction mixture in batch reactors. Therefore, Oppenauer oxidation of the Mg salt of **2a** with **1a** gave the resulting ketone **4a** and benzyl alcohol **5a**.[16] The ketone **4a** was further converted into the trimerized byproduct **3a** via aldol reaction twice.[17] To the best of our knowledge, this is the first report of a trimerized byproduct generated consecutively during addition of Grignard reagents to aldehydes. The evidence that the ketone **4a** and benzyl alcohol **5a** were detected on HPLC in comparison with authentic samples supports our mechanism considerations.

Addition of a solution of **1a** in THF to MeMgBr gave a moderate yield of **2a**, and the residual amount of **1a** increased because MeMgBr was consumed by addition of MeMgBr to the methyl ester in **2a**. The extended reaction time increased the amount of **3a** since the residual starting material **1a** reacted with the Mg salt of the target product **2a** (entry 1, Table 1). Simultaneous addition of **1a** and MeMgBr did not suppress the reaction between the starting material **1a** and the Mg salt of the target product **2a** (entry 2, Table 1).[18] The addition time of MeMgBr had a great impact on the generation of **3a**. When the addition time was extended to 60 minutes, **3a** increased to 21.5%, whereas ultrafast addition of 10 seconds minimized **3a** to 4.4% at room

temperature (entries 3-5, Table 1) by shortening the time of coexistence of **1a** and the Mg salt of **2a**. When the reaction temperature was decreased, the yield of **2a** gradually increased (entries 4, 6, 7, Table 1). Furthermore, **2a** was obtained almost quantitatively and the generation of **3a** was suppressed below 1% under cryogenic conditions (entry 7, Table 1).

Table 1. Screening of Reaction Conditions in Batch Reactors



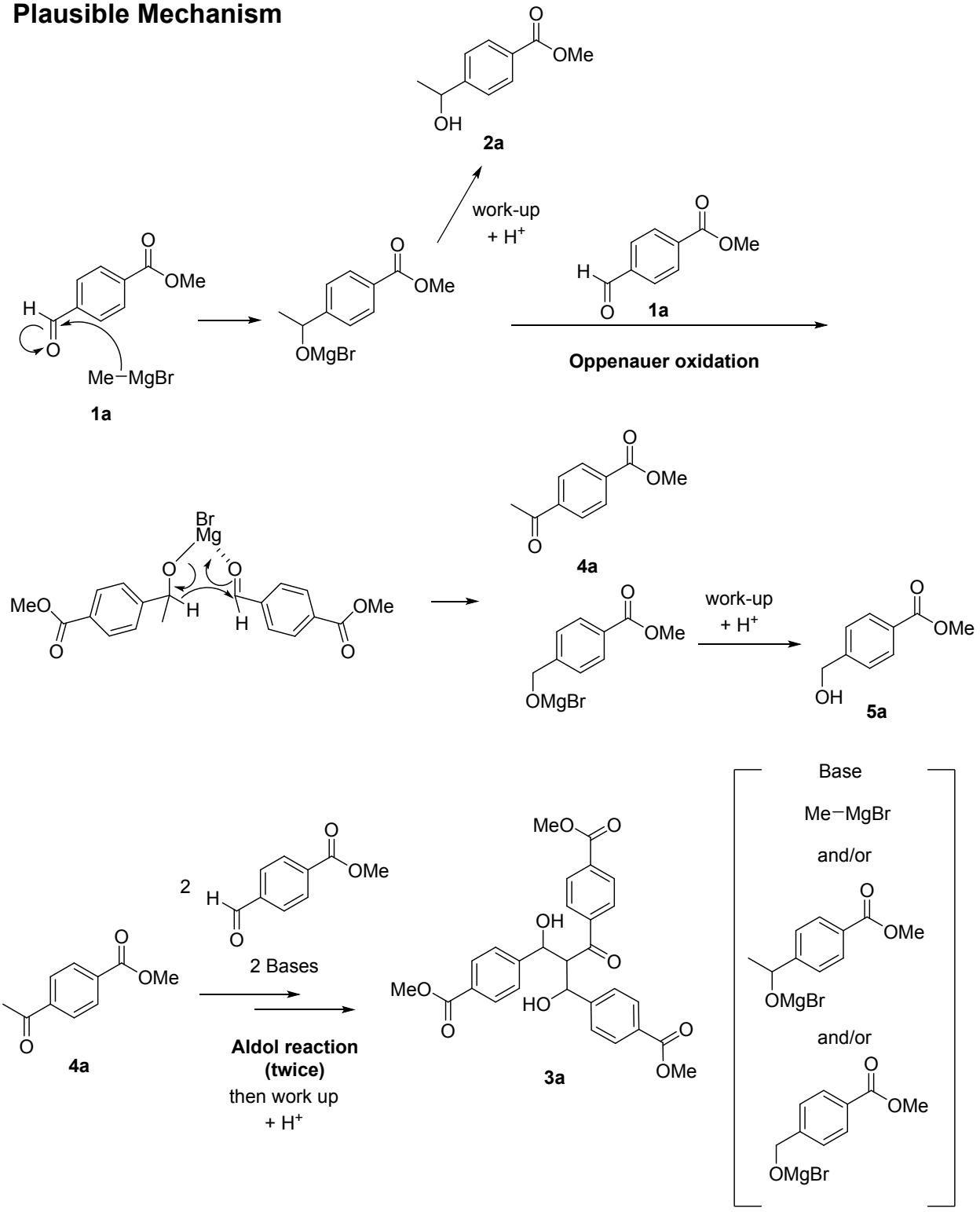
entry[a]	internal temperature	addition order addition time	reaction time	HPLC (%)[b]		
				1a	**2a**	**3a**
				RRT[c] 1.17	–	RRT 1.48
1	25°C	**1a** to MeMgBr	1 min	28	60	3.0
		10 min	10 min	13	55	13.2
2	25°C	simultaneous	1 min	32	49	14.4
			10 min	18	45	25.6
3	25°C	MeMgBr to **1a**	1 min	1	92	4.8
		10 sec	10 min	0	91	4.4
4	25°C	MeMgBr to **1a**	1 min	0	60	11.6
		10 min	10 min	0	61	10.2

5	25°C	MeMgBr to **1a**	1 min	0	28	22.3
		60 min	10 min	0	28	21.5
6	−10°C	MeMgBr to **1a**	1 min	1	77	7.8
		10 min	10 min	1	77	8.5
7	−60°C	MeMgBr to **1a**	1 min	16	85	0.8
		10 min	10 min	14	85	0.8
			30 min	16	84	0.8
	Heated to 5°C		+ 10 min	1	>99	0.7

[a] Reaction conditions: 0.50 g (3.05 mmol) – 1.10 g (6.70 mmol) of **1a**, 1.0 equiv of MeMgBr and 19–22 vol of THF based on **1a**. [b] Reaction mixtures were assayed, and yields were determined by HPLC analysis using an authentic sample. [c] RRT: Relative retention time. RRT was calculated based on the retention time of **2a.**

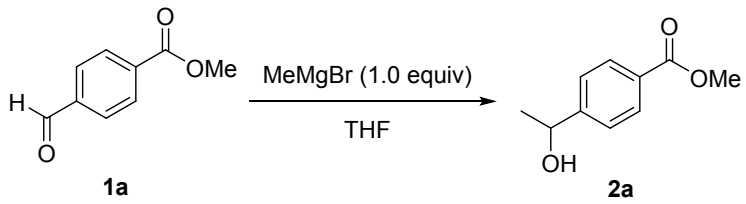
Scheme 1. Plausible Mechanism for the Generation of the Trimerized Byproduct.

Plausible Mechanism



Although the byproduct **3a** could be reduced under cryogenic conditions in conventional batch reactors, the equipment for cooling to cryogenic conditions is very limited due to the low-availability. Also, avoiding such conditions would help conserve energy costs. An alternative process to reducing the byproduct **3a** was ultrafast addition of MeMgBr at room temperature, although the scale-up to batch manufacturing would be difficult. Calorimetry analysis using RC1e[19,20] revealed that the total heat of reaction was 184 kJ/mol (Table 2), and the addition time of MeMgBr was estimated by simulations for the transition of internal temperature based on this calorimetry result for a variety of manufacturing scales (Table 3). Addition of MeMgBr could be completed within a few minutes on a 5.0 g scale of charge amount (entry 1, Table 3). Even for a charge amount of 10 kg, the addition time was estimated to be 30 minutes to maintain an internal temperature at 25±5°C due to high heat generation (entry 2, Table 3). As for a charge amount of 300 kg, the addition time would be at least 90 minutes (entry 4, Table 3). Based on these simulations, this reaction cannot be conducted at room temperature in batch manufacturing because when a larger manufacturing scale is used, a longer addition time is needed. Thus, we propose that using continuous flow synthesis would be a practical approach to solving this problem, and the fast mixing,[21] which is one advantage of continuous flow synthesis, would be effective for suppressing the byproduct **3a** regardless of the manufacturing scale.

Table 2. Calorimetry Analysis Using RC1e



1a **2a**

charge amount of **1a** (g)	reaction mass (kg)	temperature (°C)	enthalpy (kJ)	the total heat of reaction (kJ/mol)
5.0	0.048	25	5.6	184

Table 3. Estimation of Addition Time of MeMgBr by Simulation of Internal Temperature

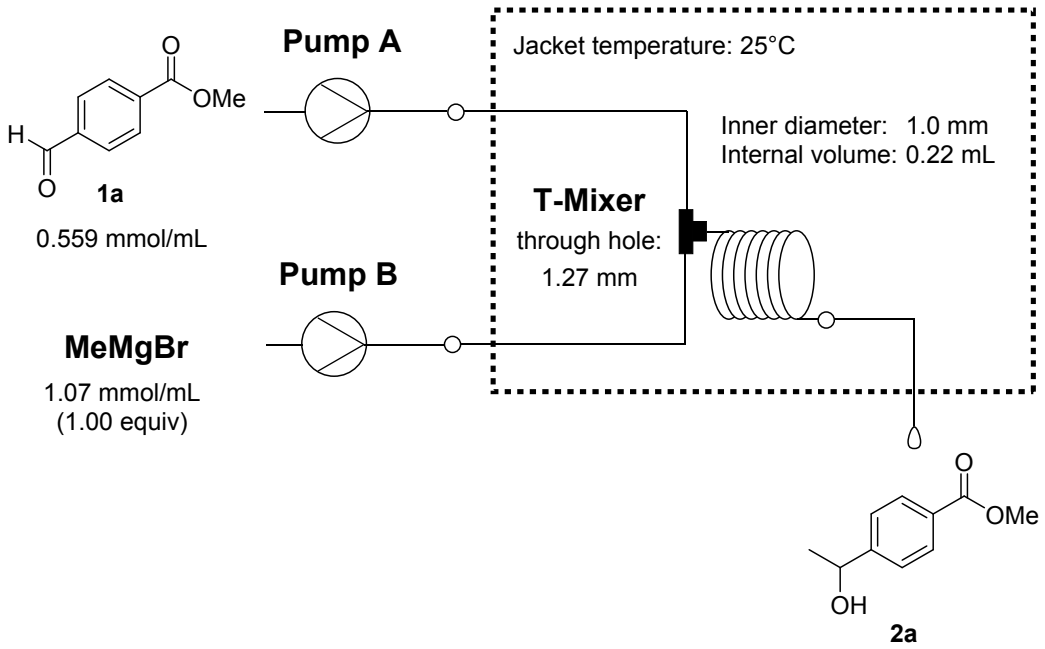
entry[a]	charge amount of **1a** (kg)	required addition time (min)
1	0.005	2
2	10	30
3	50	45
4	300	90

[a] Assumption; overall heat transfer coefficient is 150 J/m^2·K·s (measured with our manufacturing equipment). The jacket temperature is set as −20°C. The internal temperature is maintained at 25±5°C. See Supporting Information for the simulation details.

In a preliminary study of continuous flow synthesis, the inner diameter and internal volume of the tube reactor were fixed, and various flow rates were examined (Table 4). When the total flow rate was 1.66 mL/min, the largest amount of the starting material **1a** remained (20.7%, entry 1, Table 4). This revealed that the flow rate has an impact on mixing efficiency, and a low flow rate leads to low conversion in spite of a long residence time.[22] 4.98 mL/min (entry 2, Table 4), 8.30 mL/min (entry 3, Table 4) and 13.27 mL/min (entry 4, Table 4) for total flow rates provided approximately 90% yield. Therefore, conversion to the target product **2a** could be almost completed within a few seconds when the total flow rate was higher than 4.98 mL/min. In all these cases, the trimerized byproduct **3a** was drastically suppressed to 0.1% at room temperature

by the introduction of continuous flow synthesis compared with 10.2% under the standard conditions in batch reactors. The fast mixing by the application of continuous flow synthesis led to a short coexistence time of **1a** and the Mg salt of **2a**, which was effective for suppressing the byproduct **3a** as expected.

Table 4. Preliminary Screening of Flow Rate Using Continuous Flow Synthesis



entry	pump A pump B (mL/min)[a]	residence time (sec)	molecular ratio (%)[b]				
			5a	**2a**	**1a**	**4a**	**3a**
			RRT[c] 0.87	–	RRT 1.17	RRT 1.21	RRT 1.48
1	1.09 0.57	8	1.3	77.2	20.7	0.7	0.1
2	3.27 1.71	3	1.0	88.9	9.6	0.5	0.1

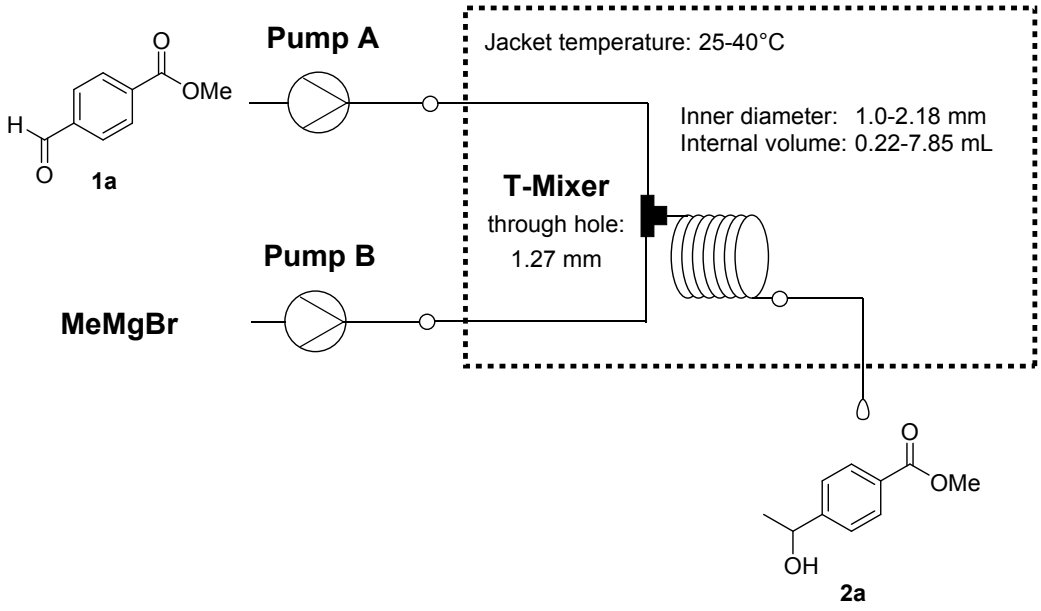
3	5.45 2.85	2	0.9	91.0	7.6	0.5	0.1
4	8.72 4.55	1	0.7	90.4	8.5	0.4	0.1
5[d]	–	–	15.9	60.7	0.2	0.1	10.2

[a] Flow rates of pump A and pump B were adjusted so that the equivalent of MeMgBr would be adjusted to 1.00 equiv. [b] Molecular ratio (**1a**,**2a**,3×**3a**,**4a**,**5a** and other impurities) was calculated by HPLC with sensitivity corrections for continuous flow synthesis. Other impurities of more than 1.0 area% were detected as the sensitivity equivalent to **2a**. Note that **3a** is composed of 3 molecules of **1a**. [c] RRT: Relative retention time. RRT was calculated based on the retention time of **2a.** [d] Result for batch conditions as reference; MeMgBr was added to a solution of **1a** at 25°C over 10 min. The reaction mixture was assayed, and yield was determined by HPLC analysis using an authentic sample.

This preliminary result encouraged us to examine the robustness of this continuous flow system for manufacturing purposes. Standard conditions were set as follows: 1.00 equiv of MeMgBr, 8.30 mL/min for total flow rate, 29 seconds of residence time, 25°C for jacket temperature, 0.559 mmol/mL for concentration of **1a**, and 1.07 mmol/mL for concentration of MeMgBr. We evaluated the acceptable ranges of the variable parameters (flow rate, temperature and concentration of reagents) (Table 5). When the residence time was 2 seconds, 29 seconds and 57 seconds, more than 90% yield was obtained. An extended residence time led to slightly higher amounts of the trimerized byproduct **3a** but the level remained suppressed at 0.5% (entries 1, 2, 3, Table 5). When the equivalents of MeMgBr were adjusted to 1.05 equiv and 1.10 equiv by adjustment of the flow rate of MeMgBr, the starting material was correspondingly consumed (entries 4, 5, Table 5), resulting in maximizing of the yield of the target product **2a** to 98.0% (entry 5, Table 5). Continuous flow synthesis at 40°C also resulted in near completion of the reaction (entry 6, Table 5). The concentration and inner diameter of the tube reactor did not have a great impact on the reaction conversion and the amount of the byproduct **3a** (entries 7, 8,

9, Table 5). These results clearly showed that the trimerized byproduct **3a** was generally suppressed to not more than 0.5% in the confirmed ranges of variable parameters with continuous flow synthesis, while temperature and addition time of MeMgBr had a great impact on generation of the trimerized byproduct **3a** in batch reactors. Furthermore, these results indicated that application of continuous flow synthesis successfully improved the process robustness compared with batch reactors. However, strict control of the flow rate is a key factor for controlling the equivalent ratio and maintaining stable reaction conversion in manufacturing by continuous flow synthesis.

Table 5. Evaluation of Process Robustness with Continuous Flow Synthesis



entry	pump A pump B (mL/min)	concentration of **1a** concentration of MeMgBr	jacket temperature (°C) inner	residence time[a] (sec)	molecular ratio (%)[b]				
					5a	**2a**	**1a**	**4a**	**3a**
					RRT[c]	–	RRT	RRT	RRT

		(mmol/mL)	diameter (mm)		0.87		1.17	1.21	1.48
1	5.45 2.85 (1.00 equiv)	0.559 1.07	25 1.0	2	0.9	91.0	7.6	0.5	0.1
2	5.45 2.85 (1.00 equiv)	0.559 1.07	25 1.0	29	1.0	91.0[e]	7.2 [e]	0.6	0.3
3	5.45 2.85 (1.00 equiv)	0.559 1.07	25 1.0	57	1.1	94.4	3.5	0.5	0.5
4	5.45 2.99 (1.05 equiv)	0.559 1.07	25 1.0	29	0.7	96.0	2.7	0.4	0.2
5	5.45 3.14 (1.10 equiv)	0.559 1.07	25 1.0	28	0.4	98.0	0.1	0.1	0.0
6	5.45 2.85 (1.00 equiv)	0.559 1.07	40 1.0	29	0.4	97.2	0.1	0.0	0.0
7	4.96 2.85 (1.00 equiv)	0.615 1.07	25 1.0	31	0.9	93.6	5.0	0.4	0.2

8	5.97 2.85 (1.00 equiv)	0.511 1.07	25 1.0	27	1.1	89.2	8.9	0.6	0.1
9	5.45 2.85 (1.00 equiv)	0.559 1.07	25 2.18	29	1.1	91.8	6.2	0.6	0.3
10[d]	–	–	25	–	15.9	60.7	0.2	0.1	10.2

[a] The internal volume was 4.04 mL (entries 2, 4–9), 0.22 mL (entry 1) and 7.85 mL (entry 3). [b] Molecular ratio (**1a**, **2a**, 3×**3a**, **4a**, **5a** and other impurities) was calculated by HPLC with sensitivity corrections in continuous flow synthesis. Other impurities of more than 1.0 area% were detected as the sensitivity equivalent to **2a**. Note that **3a** is composed of 3 molecules of **1a** [c] RRT: Relative retention time. RRT was calculated based on the retention time of **2a.** [d] Result for batch conditions as reference; MeMgBr was added to a solution of **1a** at 25°C over 10 min. Reaction mixture was assayed, and the yield was determined by HPLC analysis using an authentic sample. [e] Isolated yield was also confirmed in entry 2. The yield of **2a** and recovery of **1a** were 91% and 8%, respectively.

Running for a long duration was demonstrated to confirm the robustness of this continuous flow system. The transition of the reaction conversion was analyzed in running for 6 hours as shown in Table 6. The reaction conversions did not change for 6 hours, which indicated that this continuous flow system has an acceptable robustness.

Table 6. Transition of the reaction conversion in running for a long duration

entry[a]	running time (min)	molecular ratio (%)[b]				
		5a	**2a**	**1a**	**4a**	**3a**
		RRT[c] 0.87	–	RRT 1.17	RRT 1.21	RRT 1.48

1	5	0.4	96.8	0.1	0.0	0.0
2	60	0.5	96.2	0.2	0.0	0.0
3	120	0.2	96.5	0.1	0.0	0.0
4	180	0.3	96.7	0.1	0.0	0.0
5	240	0.3	97.0	0.1	0.0	0.0
6	300	0.3	96.8	0.1	0.0	0.0
7	350	0.3	96.9	0.1	0.0	0.0

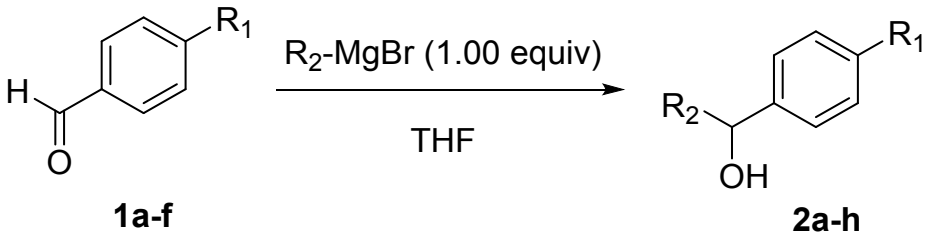
[a] Jacket temperature was 25°C, inner diameter was 1.0 mm, internal volume was 2.14 mL, and T-mixer (through hole 1.27 mm) was used. Flow rate of pump A (solution of **1a**, 0.559 mmol/mL) was 3.27 mL/min, Flow rate of pump B (MeMgBr) was 1.97 mL/min in the case of 1.02 mmol/mL, and 1.90 mL/min in the case of 1.06 mmol/mL (1.10 equiv). The residence time was calculated as 25 sec. [b] Molecular ratio (**1a**, **2a**, 3×**3a**, **4a**, **5a** and other impurities) was calculated by HPLC with sensitivity corrections in continuous flow synthesis. Other impurities of more than 1.0 area% were detected as the sensitivity equivalent to **2a**. Note that **3a** is composed of 3 molecules of **1a** [c] RRT: Relative retention time. RRT was calculated based on the retention time of **2a.**

The productivity of the target product **2a** using this continuous flow system was estimated. When the maximum flow rate as shown in entry 4 in Table 4 is demonstrated, the fed amount of **1a** is estimated to be 1.2 kg/day, which gives 1.2 kg/day of **2a**.[23] If ten pieces of this continuous flow system are connected in parallel, the productivity will be 12 kg/day, which has an appropriate productivity for pilot manufacturing in an early phase. Further investigations into running for a longer duration, and scale-up such as lager tubes, higher flow rates or larger dimensions of mixers are ongoing.

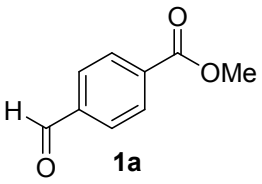
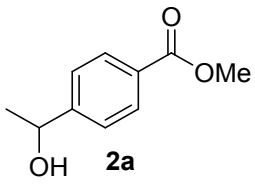
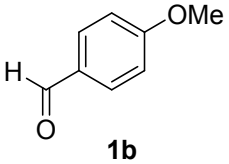
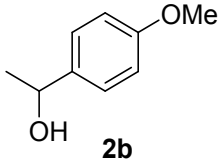
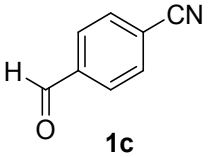
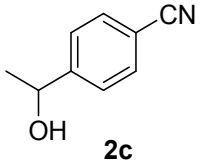
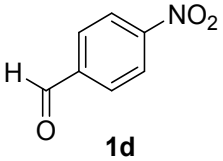
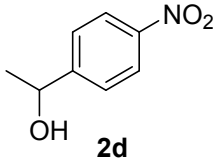
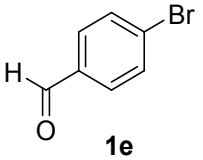
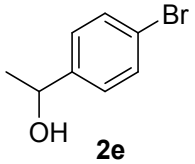
This reaction system was applied to other similar reactions (Table 7). The difference of yield between batch and flow procedures was evaluated. First, benzaldehyde derivatives containing a variety of functional groups were examined. An electron-rich substrate bearing methoxy group **1b** resulted in high yields for both batch and flow procedures since Oppenauer oxidation was

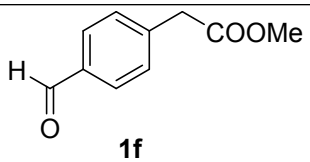
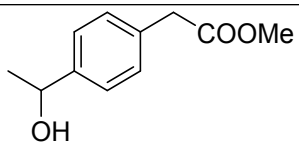
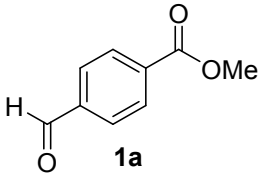
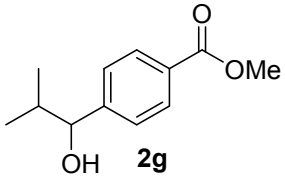
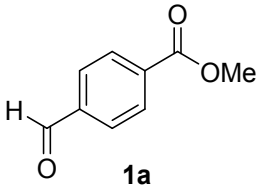
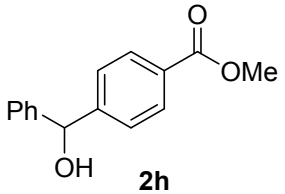
suppressed even under batch conditions (entry 2, Table 7). With 4-cyanobenzaldehyde **1c** and 4-nitrobenzaldehyde **1d**, batch procedures provided a moderate yield to low yield due to the complex mixtures, and precipitation was observed in batch procedures (entries 3 and 4, Table 7), for which the flow procedure could not be evaluated. Examining 4-bromo benzaldehyde **1e** and methyl (*p*-formylphenyl) acetate **1f** bearing α-hydrogen showed that application of the flow procedure improved the yield of **2e** and **2f** by approximately 20% (entries 5 and 6, Table 7). When **1f** was used as the substrate, approximately 10% of the residual starting material was observed, probably due to deprotonation at the α-position by MeMgBr (entry 6, Table 7). Next, Grignard reagents were examined. ^{i}PrMgBr was allowed to react with methyl 4-formyl benzoate (**1a**), and the generation of byproducts derived from Oppenauer oxidation was suppressed by the application of a flow condition, resulting in improvement of the yield of **2g** (27% (Batch) to 51% (Flow)). However, the reduction of **1a** could not be suppressed sufficiently by application of flow procedure to give the target product **2g** in a moderate yield (51%, entry 7, Table 7) since reduction of **1a** by β-hydride reduction[24] was competitive with the addition of ^{i}PrMgBr to **1a**. For addition of PhMgBr, application of continuous flow synthesis also improved the yield compared with the batch procedure, and the flow procedure afforded nearly the quantitative yield of **2h** (entry 8, Table 7). Consequently, the application of continuous flow synthesis generally provided improvement of yields for addition of Grignard reagents to aromatic aldehydes compared with the batch procedure, which should be a practical approach to these reaction systems.[25]

Table 7. Application of Continuous Flow Synthesis in a Variety of Substrates and Grignard Reagents



1a-f **2a-h**

entry	substrate	Grignard reagent	product	procedure[a]	yield (%)[b]
1	 **1a**	MeMgBr	 **2a**	Batch	61
				Flow	91
2	 **1b**	MeMgBr	 **2b**	Batch	88
				Flow	92
3	 **1c**	MeMgBr	 **2c**	Batch	50
				Flow	–[c]
4	 **1d**	MeMgBr	 **2d**	Batch	3
				Flow	–[c]
5	 **1e**	MeMgBr	 **2e**	Batch	77
				Flow	97

6	 **1f**	MeMgBr	 **2f**	Batch	57
				Flow	79
7	 **1a**	^{i}PrMgBr	 **2g**	Batch	27
				Flow	51
8	 **1a**	PhMgBr	 **2h**	Batch	79
				Flow	99

[a] Batch; Grignard reagents were added to a solution of **1a-f** at 25°C over 10 min. Flow: jacket temperature was 25°C, inner diameter was 1.0 mm, internal volume was 4.04 mL, and T-mixer (through hole 1.27 mm) was used. [b] Batch: Reaction mixture was assayed, and yield was determined by HPLC analysis using an authentic sample. Flow: Isolated yield. [c] Not conducted due to precipitation.

CONCLUSION

In conclusion, we established a practical synthetic approach for addition of MeMgBr to methyl 4-formyl benzoate (**1a**) using continuous flow synthesis. The unexpected trimerized byproduct **3a** was drastically suppressed to not more than 0.5%, and the yield was greatly improved to 98% at room temperature. In the ranges of variable parameters, the trimerized byproduct **3a** was generally suppressed, and the robustness of this procedure was confirmed. This approach was widely applied to other addition reactions of Grignard reagents to aromatic aldehydes, with confirmation of a general improvement of the yield using the proposed procedure. It can be widely used when byproducts are generated by reaction between the starting material and the target product in batch manufacturing during addition of a reagent; the key to success is reduction of the addition time. Our next challenge is to apply in-line monitoring to control

reaction rate by in-situ Fourier Transform Infrared Spectroscopy (FT-IR) in a flow system and to use internal temperature monitoring to enable reliable internal temperature simulations[26] for process safety. Our final goal is the realization of continuous manufacturing of drug substances by continuous flow synthesis.

EXPERIMENTAL SECTION

General Information

All reactions were run under a nitrogen atmosphere. Solvents and reagents were purchased from commercial sources and used without further purification. **1a** and ^{i}PrMgBr in THF were purchased from Tokyo Chemical Industry Co., Ltd. MeMgBr in THF and PhMgBr in THF were purchased from Kanto Chemical Co., Inc. Because a metallic precipitate was often observed in commercial Grignard reagents, the precipitate should be dissolved carefully at 40°C before using commercial Grignard reagents to avoid an unexpected clogging in continuous flow synthesis. High performance liquid chromatographic (HPLC) analysis was carried out using a Shimadzu LC-2010CHT. The heat of reaction was measured using Mettler Toledo RC1e. ^{1}H NMR, ^{13}C NMR, and 2D NMR spectra were recorded on a Bruker Avance III HD 400 MHz. LCMS were recorded on a Shimadzu LCMS-2010EV. A T-shape mixer was purchased by M&S Instruments Inc. (P-633, through hole 0.05 inch (= 1.27 mm)). The Vapourtec V-3 is a peristaltic pump.

Flow rates were calibrated manually as follows: the weight of the fed amount was measured for 1 minute using THF in the case of pump A and MeMgBr in THF (1.07 mmol/mL) in the case of pump B. The measured weight was converted to the volume using the density.

Dimethyl 4,4'-(1,3-dihydroxy-2-(4-(methoxycarbonyl)benzoyl)propane-1,3-diyl)dibenzoate (3a)

Two solutions were fed by the Vapourtec V-3; solution A was a solution of **1a** in 10 volumes of THF (0.559 mmol/mL) and solution B was MeMgBr in THF (1.07 mmol/mL). Flow rate of solution A was set as 1.09 mL/min, and that of solution B was set as 0.57 mL/min so that the equivalent of MeMgBr would be adjusted to 1.00 equiv. Two solutions were poured into a 4-neck flask containing THF (10 mL) with a stirring bar at 25°C for 11 minutes. Input amount of the starting material **1a** was defined as 1.10 g (0.559 mmol/mL × 1.09 mL/min × 11 min × 164.16 mg/mmol). The reaction mixture was stirred for 90 minutes and poured into the mixture of ethyl acetate (80 mL) and aqueous solution of citric acid prepared from citric acid monohydrate (2.0 g) and water (38 mL) at 0°C. The organic phase was separated, and the organic phase was washed with water (20 mL). The organic phase was evaporated, and the residue was purified by flash column chromatography on silica gel (eluent: *n*-hexane/ethyl acetate 75/25 (v/v) to 60/40 (v/v)) to afford **3a** (74.2 mg, 95.2 area%, containing ethyl acetate (1 wt%) and *n*-hexane (2 wt%) from ^{1}H-NMR). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93–7.90 (6H, m), 7.68–7.66 (2H, m), 7.41–7.39 (4H, m), 5.02 (2H, dd, J = 6.3, 6.3 Hz), 4.08 (1H, t, J = 6.2 Hz), 3.89 (3H, s), 3.87 (6H, s), 3.78 (2H, d, J = 6.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 205.77, 166.76, 166.13, 146.82, 141.63, 134.17, 129.99, 129.95, 129.69, 128.21, 126.01, 74.17, 59.25, 52.27, 52.25. MS (ESI^+) m/z 529 $[M+Na]^+$.

Calorimetry analysis procedure

Two solutions were fed by the Vapourtec V-3; solution A was a solution of **1a** in 10 volumes of THF (0.559 mmol/mL) and solution B was MeMgBr in THF (1.07 mmol/mL). Flow rate of

solution A was set as 5.45 mL/min, and that of solution B was set as 2.85 mL/min so that the equivalent of MeMgBr would be adjusted to 1.00 equiv. Two solutions were mixed at a T-shape mixer, and the combined solution was passed through PFA tube reactors (inner diameter 1.0 mm, internal volume 7.85 mL). The flow system consisting of the T-mixer and the tube reactor was put in RC1e and RC1e was filled with water (475 mL). The filled water was adjusted to 25°C, and heat generation was measured for 10 minutes. Input amount of the starting material **1a** was defined as 5.00 g (0.559 mmol/mL × 5.45 mL/min × 10 min × 164.16 mg/mmol)

General procedure of continuous flow synthesis to synthesize 2a in Table 4

Two solutions were fed by the Vapourtec V-3; solution A was a solution of **1a** in 10 volumes of THF (0.559 mmol/mL) and solution B was MeMgBr in THF (1.07 mmol/mL). Flow rate of solution A was set as 1.09 mL/min to 8.72 mL/min, and that of solution B was set as 0.57 mL/min to 4.55 mL/min so that the equivalent of MeMgBr would be adjusted to 1.00 equiv. Two solutions were mixed at a T-shape mixer in a bath of 25°C, and the combined solution was passed through PFA tube reactors (inner diameter 1.0 mm, internal volume 0.22 mL). After reaching a steady state (running for 3 minutes), the reaction mixture was poured into MeCN/H_2O (80/20 (v/v)) containing 0.1 vol% of HCOOH directly and diluted in a measuring flask to measure the molecular ratio (**1a**, **2a**, 3×**3a**, **4a**, **5a** and other impurities).

Isolating procedure of 2a–h using continuous flow synthesis

Two solutions were fed by the Vapourtec V-3; solution A was a solution of **1a–f** in THF (adjusted to 0.559 mmol/mL) and solution B was MeMgBr in THF (1.07 mmol/mL), ^{i}PrMgBr in THF (1.0 mmol/mL) or PhMgBr in THF (1.07 mmol/mL). Flow rate of solution A was fixed as

5.45 mL/min, and that of solution B was adjusted so that the equivalent of MeMgBr, ^{i}PrMgBr and PhMgBr would be adjusted to 1.00 equiv. Two solutions were mixed at a T-shape mixer in a bath of 25°C, and the combined solution was passed through PFA tube reactors (inner diameter 1.0 mm, internal volume 4.04 mL). After reaching a steady state (running for 3 minutes), the reaction mixture was poured into the mixture of ethyl acetate (100 mL) and aqueous solution of citric acid prepared from citric acid monohydrate (0.96 g) and water (100 mL) at 0°C for 2 minutes. The organic phase was separated, and the aqueous phase was extracted with ethyl acetate (50 mL). The combined organic phases were evaporated, and the residue was purified by flash column chromatography on silica gel (eluent: *n*-hexane/ethyl acetate 90/10 (v/v) to 70/30 (v/v)) to afford the target product **2a–h**. Input amount of the starting materials depends on molecular weight (0.559 mmol/mL × 5.45 mL/min × 2 min × molecular weight mg/mmol)

Methyl 4-(1-hydroxyethyl)benzoate (2a)

Input amount of the starting material: 1000.2 mg. Isolated amount of recovery **1a** and **2a** were 80.2 mg (8%, 92 area%, containing 8 area% of **5a**) and 1002.0 mg (91%, 99.3 area%), respectively. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.99–7.96 (2H, m), 7.42–7.40 (2H, m), 4.92 (1H, qd, J = 6.5, 3.0 Hz), 3.89 (3H, s), 2.48 (1H, d, J = 3.1 Hz), 1.48 (3H, d, J = 6.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.13, 151.17, 129.90, 129.19, 125.38, 69.97, 52.16, 25.34. MS (ESI^+) m/z 163 $[M-OH]^+$.

ASSOCIATED CONTENT

Supporting Information

HPLC Methods for preparation of **2a**–**h** and **3a**, procedures of batch synthesis to synthesize **2a**, ^{1}H NMR spectra and ^{13}C NMR spectra of **2a–h** and **3a**. 2D-NMR (COSY, HSQC, HMBC) spectra of **3a**, heat flow about addition of MeMgBr and data for justification of calorimetry analysis combined with continuous flow system and RC1e, simulation details based on the heat of reaction, a detailed description of the equipment used for continuous flow synthesis, procedure of running for a long duration

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Notes

The authors declare no competing financial interest.

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[23] The fed amount of **1a** was calculated as follows: 0.559 (mmol/mL) × 8.72 (mL/min) × 164.16 (mg/mmol) × 60 × 24 ÷ 1000000 = 1.15 kg/day. The productivity of **2a** was calculated as follows: 1.15 (kg/day) × 180.20/164.16 × 95/100 (estimated yield) = 1.20 (kg/day).

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[25] Although commercially available Grignard reagents were utilized in this work, preparations of a wide variety of Grignard reagents using ^{i}PrMgCl·LiCl have been investigated. See, Brodmann, T.; Koos, P.; Metzger, A.; Knochel, P.; Ley, S. V. Continuous Preparation of Arylmagnesium Reagents in Flow with Inline IR Monitoring. *Org. Process Res. Dev.* **2012**, *16*, 1102–1113.

[26] Asano, S.; Yatabe, S.; Maki, T.; Mae, K. Numerical and Experimental Quantification of the Performance of Microreactors for Scaling-up Fast Chemical Reactions. *Org. Process Res. Dev.* **2019**, *23*, 807–817.