**Doctoral dissertation**

# Living Anionic Monoaddition of Organometals Using Flow Microreactors

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# Contents

# Chapter 1

# General Introduction

## 1-1. Sequence-defined polymers

Sequence-defined macromolecules represent a unique class of monodisperse oligomers or macromolecules, wherein different monomer units are placed in exact positions [1]. Sequence-defined polymers in nature, such as DNA and proteins, perform a wide array of essential functions critical for the maintenance of life. DNA serves as a repository for genetic information, functioning as a biological information storage system. By utilizing four nucleotide units (adenine, guanine, cytosine, thymine, or uracil), it stores biological information through macromolecular chains, each composed of a unique sequence. Furthermore, proteins can be synthesized using 20 amino acids, each conferring distinct properties, to produce a variety of proteins with specialized functions. The structural characteristics of natural high-performance polymers are inherently designed by three-dimensional molecular space. The linear arrangement of various sequence units at the molecular level enables the formation of higher-order structures based on molecular self-assembly, driven by inter- and intramolecular interactions. This process ultimately defines a distinct molecular space [2].

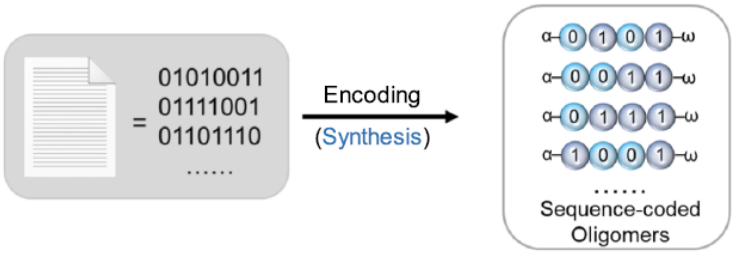


**Figure 1.** Concept of coding macromolecules by using sequence-defined polymers

Inspired by the primordial strategies in nature, organic synthetic approaches aimed at the selective and continuous synthesis of sequence-defined oligomers have garnered attention as a promising strategy for realizing molecular coding [3]. Although absolute sequence control can be achieved through chemical or biological methods using multistep growth mechanisms [4], this has largely been limited to the reproduction or synthesis of mimetics of sequence-defined biopolymers [5]. As a result, most sequence-defined polymers possess phosphate-sugar or amide-based backbones [6], while copolymer synthesis with carbon-carbon bond-based backbones results in monomer sequences that are either uncontrolled or inadequately controlled. Therefore, unlike the limited monomer units found

in nature, if synthetic methods to produce sequence-defined polymers can be established using a variety of artificial monomers, molecules with vast structural diversity and functionality could be obtained (Figure 1).

## 1-2. Flow microreactor

Continuous-flow reactors are devices in which reactions proceed spatially while reactants are supplied continuously [7], and they have recently become important tools in the fields of synthetic chemistry and chemical engineering [8]. In particular, flow microreactors that employ micrometer-scale channels are regarded as technologies capable of overcoming several limitations of conventional batch reactors, owing to their superior mixing efficiency, precise control of residence time, and advanced temperature-control capabilities (Figure 2).

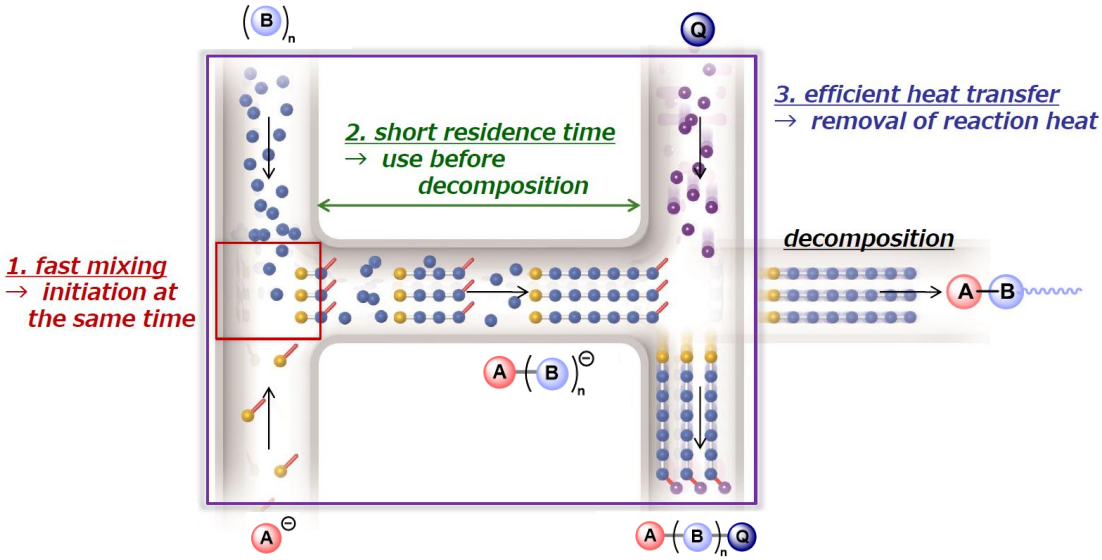


**Figure 2.** General flow microreactor system.

1. The efficiency of mixing

In chemical reactions, mixing of reactants is an important factor that determines product selectivity. In batch reactors, mixing is achieved by stirring; however, as reactor size increases, mixing becomes slower, leading to concentration gradients. These concentration gradients can cause overreaction and increase the occurrence of side reactions. In contrast, microscale flow devices enable millisecond-level mixing owing to their short diffusion distances, and strong vortices formed at the confluence of reactant streams promote efficient mixing. This rapid mixing suppresses transient concentration gradients and thereby effectively reduces decomposition, overreaction, and side reactions [9]. This advantage is particularly important when handling highly reactive intermediates such as organometallic species, as slow mixing can lead to side reactions with the solvent or self-reactions. In

flow systems, these intermediates are homogeneously dispersed immediately upon formation and rapidly transported to the subsequent reaction stage, allowing for more precise reaction control [10].

2. Residence Time Control

In batch reactions, the reaction time is defined as the period from reagent addition to quenching. However, the actual reaction time depends on the mixing rate, and in large-scale reactors, the time required to achieve a homogeneous solution makes it difficult to accurately define the reaction time. In contrast, in flow reactors, the reaction proceeds as the mixture flows through the reactor, and the reaction time is defined as the residence time, which can be calculated from the reactor volume and flow rate and adjusted over a wide range—from milliseconds to several minutes—by controlling the pump flow. Such precise control of residence time is important for reactions involving unstable intermediates that form and decompose within a short timescale, and the narrow distribution of reaction times leads to high experimental reproducibility [11].

3. Temperature Control

Reaction rates, equilibria, and product selectivity are strongly dependent on temperature. Flow microreactors have small channel diameters and high surface-area-to-volume ratios, enabling highly efficient heat transfer. This allows rapid removal of heat generated during reactions and helps maintain relatively uniform temperatures throughout the reactor [12]. In addition, distinct temperature regions can be created within the reactor, allowing precise control in which elevated or reduced temperatures are applied only at specific stages. This level of temperature control stabilizes the reaction mixture while dynamically adjusting operating conditions to promote selective reactions [13].

## 1-3. Integrated flow microreactor system

The reaction steps can be expanded simply by connecting multiple micromixers and microreactors. This approach allows for the omission of intermediate product isolation and purification steps, and modifications to reaction conditions can be made with minimal modification. Among these, the linear integration method involves the sequential injection of reactants, with the reactions proceeding in order. For example, as shown in Figure 3, six reaction steps can be integrated into a single flow process to build a pharmaceutical structure starting from 1,3,5-tribromobenzene [14]. Based on this characteristic, there is potential for synthesizing sequence-defined polymers using multistep growth polymerization.

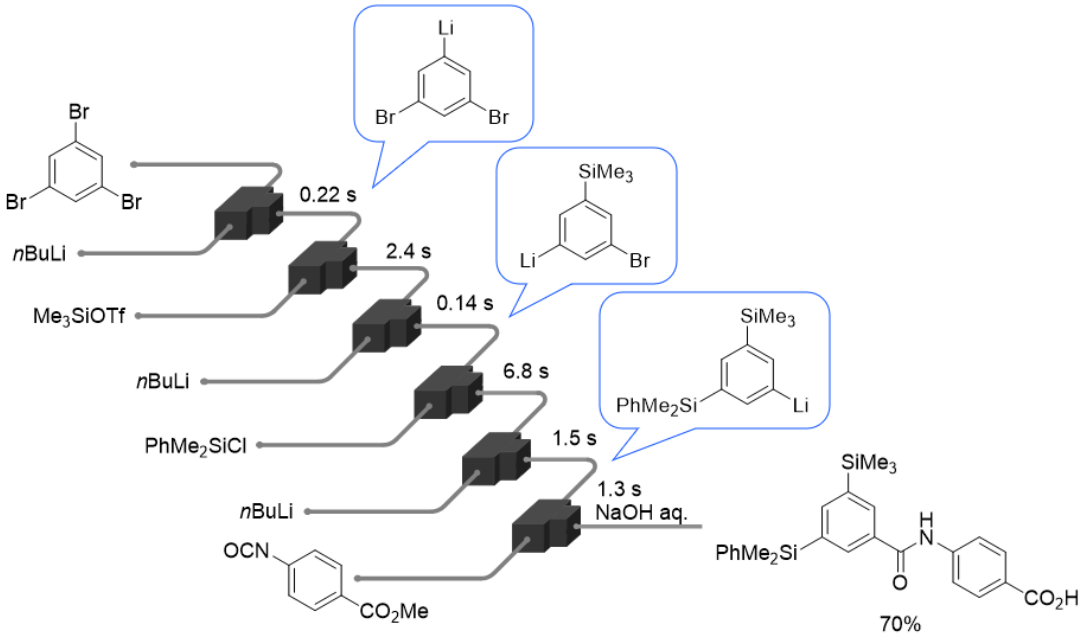


**Figure 3.** Synthesis of TAC-101 from 1,3,5-tribromobenzene using integrated flow micro system.

## 1-4. Flash-flow living anionic polymerization in polar solvent

Living anionic polymerization is one of the key reactions in polymer synthesis.[15] The polymer chain end retains living anionic activity without the need for a capping agent, thereby allowing the synthesis of polymers with complex structures. However, in batch macro-reactors using polar solvents, the reaction can be controlled at extremely low temperatures, such as -78 ℃.

In contrast, it has been reported that living anionic polymerization can be controlled under milder temperature conditions (0 ℃) even under polar solvents when using a flow microreactor.[16]

Under flow microreactor conditions, a solution of styrene dissolved in THF and a solution of sec-Butyllithium dissolved in hexane were rapidly mixed in a T-shaped micromixer (M), and the polymerization was subsequently carried out in a microtube reactor. The reaction was terminated with MeOH at the reactor outlet, resulting in the synthesis of polystyrene with a controlled molecular weight of $M_n$ = 1200–20,000 and a narrow molecular weight distribution ($M_w/M_n$ = 1.09-1.13) (Figure 4) [17].

Additionally, living anionic polymerization of alkyl methacrylate, a vinyl monomer with an ester substituent, was controlled under polar solvents. Using 1,1-diphenylhexyllithium as the initiator, living anionic polymerization of alkyl methacrylate was carried out under mild temperature conditions, affording poly(alkyl methacrylate) (PAMA) with a controlled molecular weight distribution [18].

This microflow system allows for uniform initiation reactions due to the rapid mixing of the initiator and monomer, and the suppression of overreaction due to the immediate removal of reaction heat via efficient heat transfer. Furthermore, controlling the flow rate ratio of the initiator and monomer allows

for molecular weight control.

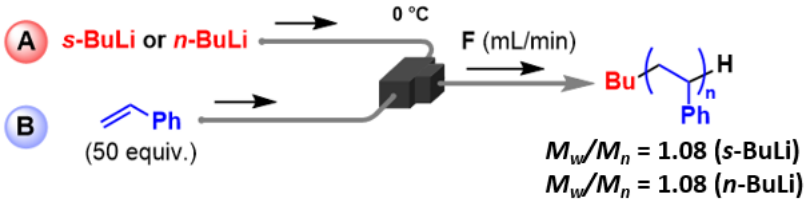


**Figure 4.** Living anionic polymerization of styrene using flow microreactors

## 1-5. Living anionic block copolymerization using an integrated flow system

The synthesis of copolymers using living anionic polymerization can be carried out by integrated flow microreactors. In other words, multistep syntheses of structurally well-defined polymers, such as end-functionalized polymers or block copolymers, can be performed in a one-flow process while maintaining the living chain-end reactivity.

An integrated flow microreactor system capable of controlled anionic polymerization of both styrene and alkyl methacrylate was used to synthesize a styrene-alkyl methacrylate di-block copolymer. The polystyrene living end generated by the anionic polymerization of styrene initiated with *sec*-butyllithium can be trapped with 1,1-diphenylethylene. The organolithium species formed through this reaction acts as the initiator for the subsequent anionic polymerization of alkyl methacrylate. As a result, a styrene-alkyl methacrylate di-block copolymer could be synthesized at controlled molecular weights under mild temperature conditions (24-28 °C) [19] (Figure 5).

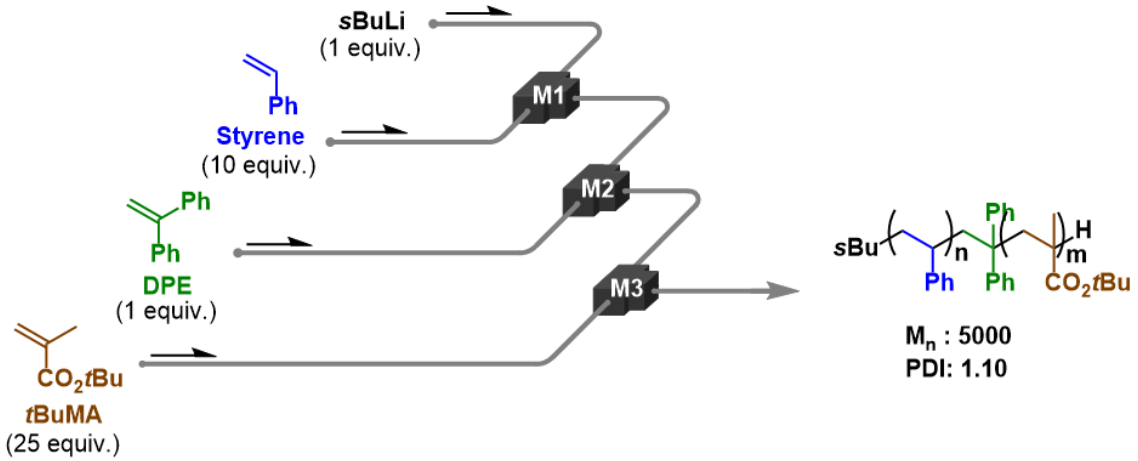


**Figure 5.** Synthesis of block copolymers using integrated flow microreactors

## 1-6. Overview

Sequence-defined polymers are macromolecules with monomers arranged in a precise sequence, providing unique functionalities. Inspired by nature's molecular coding strategies, the selective synthesis of sequence-defined oligomers has gained significant attention. However, achieving precise sequence control in carbon-carbon bond-based backbones remains challenging.

We use a flow microreactor to achieve living anionic polymerization and controlled molecular-weight distributions with methacrylates and styrene-based monomers. Additionally, we demonstrate the synthesis of block copolymers using integrated flow microreactors. This approach provides a versatile platform for controlled synthesis of sequence-defined polymers, advancing molecular coding and functional material development.

In Chapter 1, the prospects of synthesizing sequence-defined polymers were discussed based on examples of biological sequence-defined polymers. The characteristics of flow microreactors and the utility of integrated flow synthesis were outlined, with a focus on the synthesis of copolymers through controlled living anionic polymerization.

In chapter 2, styrene and methacrylate esters, as representative vinyl monomers, were T-mixed with a stoichiometric amount of organic lithium initiator in a flow microreactor. In high flow-rate regions, where sufficient mixing efficiency was expected, oligomerization was significantly suppressed, and the 1:1 monoadduct, resulting from the reaction between the initiator and vinyl monomer, was selectively obtained. Additionally, the synthesis of 1:1:1 monoadducts was successfully achieved by selectively introducing various electrophiles to the terminus of the anionic intermediate. Using this method, sequential introduction of initiators, multiple vinyl monomers, and terminal electrophiles in the flow microreactor enabled the synthesis of sequence-defined oligomers with up to six components in a short time and with high yields (Figure 6). This synthetic method is not limited to single-molecule synthesis but also allows for the introduction of specific units as oligomers while maintaining the sequence-defined regions.

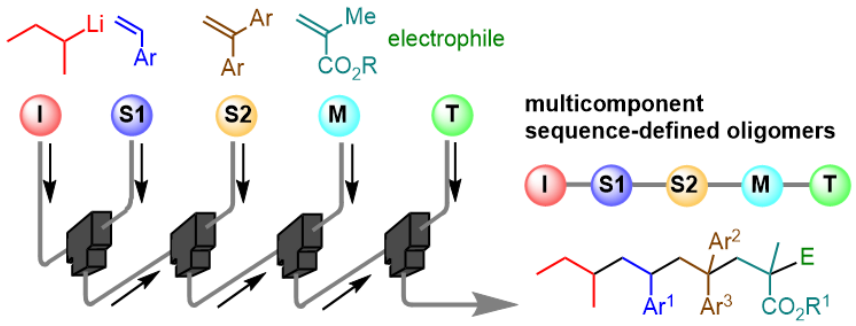


**Figure 6.** Sequence-defined synthesis enabled by fast and living anionic monoaddition of vinyl monomers

In Chapter 3, a method is presented for the fast and selective generation of benzophenone dianions (BPDs) under microflow conditions using metal naphthalenides (MNp, M = Li, K), and their application as initiators for living anionic polymerization and monoaddition reactions. By reacting lithium naphthalenide stoichiometrically with benzophenone derivatives, lithium benzophenone dianions were generated, which then underwent highly selective 1:1 monoaddition reactions with methacrylates. Flash-flow mixing minimized side reactions, enabling the selective formation of chain-type monoaddition products with high yield (Figure 7). Additionally, this method demonstrated a broad substrate scope for various benzophenone derivatives and methacrylates, and allowed for the synthesis of multicomponent coupling products and sequence-defined oligomers. This study achieves versatile synthesis based on benzophenone dianion chemistry.

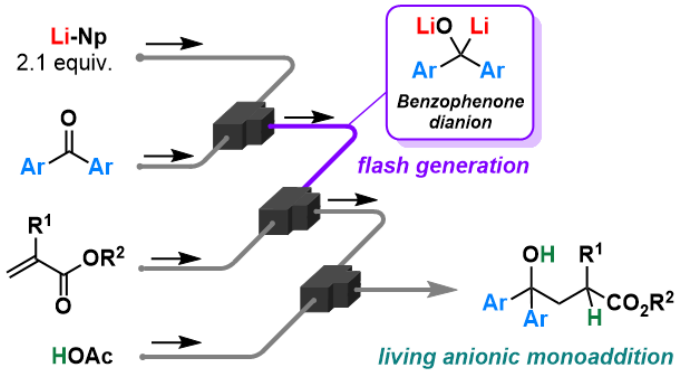


**Figure 7.** Flow-controlled living anionic monoadditional reaction initiated by flash-generated benzophenone dianions

In Chapter 4, polyesters obtained through the ring-opening polymerization (ROP) of lactones are biodegradable, making them environmentally friendly alternatives to conventional plastics. These materials have attracted significant attention and are widely studied in the chemical sciences. However, the ring-opening polymerization using various organic bases and amphoteric metal bases requires careful consideration of side reactions and terminal functional groups. To address these issues, we employed fast and irreversible anionic ring-opening polymerization to control initiation reactions and suppress side reactions. In this study, we utilized the high-speed mixing and reaction quenching functions of a flow microreactor, along with precise temperature control, to achieve controlled anionic initiation by selective nucleophilic addition to lactones using organopotassium species (Figure 8). This reaction system allowed for selective ring-opening initiation, even when using substituted organopotassium species or various lactones, and further demonstrated that polymerization could be controlled in high-speed flow systems by adjusting the excess of lactone monomers.

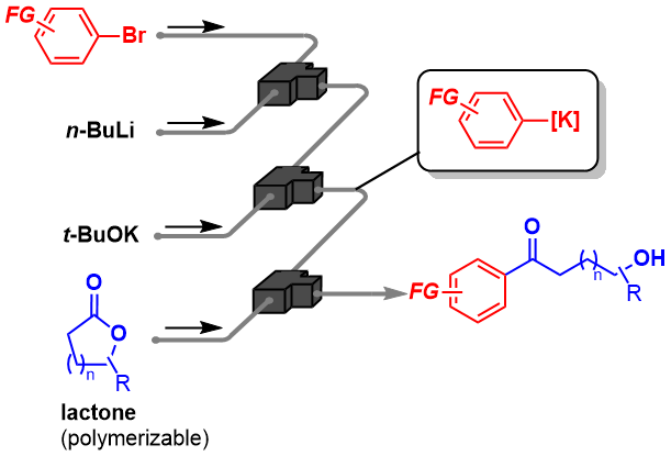


**Figure 8.** Flash-flow generation and selective monoaddition of organopotassium species to lactones

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# Chapter 2

# Sequence-Defined Synthesis Enabled by Fast and Living Anionic Monoaddition of Vinyl Monomers

## 2-1. Introduction

The discovery of macromolecules and synthetic establishment of polymers in industry have brought dramatic improvements of convenience in our society from the 20$^{th}$ century, enabling massive production of textile goods that had only been produced from biomaterials, other necessities of life, and advanced materials sustaining pioneering industries. Up to the present, the use of polymers has been divergent into petrochemical fundamentals, medicinal-related compounds, electronic materials, and so on. Considering the macro-molecularity in terms of the polymer functions, the structural characteristics of natural functional macromolecules like sugars, proteins, and nucleic acids are inherently designed by their three-dimensional molecular space. Linear arrangement of various sequence units one by one at the unimolecular level generates a definite molecular space based on their higher-order structures, which are formed by molecular self-assembly through both their inter- and intra-molecular interactions.[1] Such primeval strategy of nature leads to the acquirement of unique functions in higher forms of life that have not yet been achieved by artificial molecules. While chemical or biological synthesis for fully sequence-defined molecules based on the current technology is limited to biomolecules or their mimics, the author notes that attempts at the organic synthesis of artificially sequence defined oligomers in a selective and continuous manner have recently attracted much attention for the achievement of "molecular coding".[2] Nature uses the limited number of monomer units (20 amino acids or 4 types of nucleobases) to achieve molecular coding or structural diversities. If the author achieves the artificial version of the sequence-defined polymers, infinite diversities of encoded molecules could be synthesized.

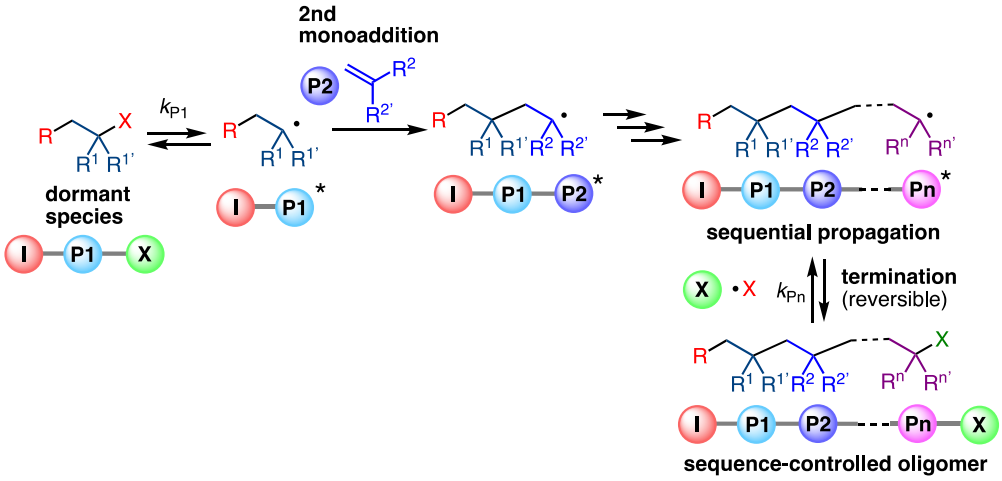
Industrially established macromolecular chemistry utilizing typical vinyl monomers like styrenes and methacrylates is recognized as fundamental methodology to construct functional macromolecules.[3] However, practical sequential addition system utilizing such vinyl monomers is currently limited to the relatively "slow" reactions to suppress the uncontrolled polyaddition as a side reaction, but the precise control of "fast" reactions are rather suitable for constructing sequence-defined oligomers because of monomer diversity as well as productivity. Once the author has a both precise and fast synthetic method for sequenced artificial molecules in hand, such methodology will provide an opportunity to create the novel functions that could not be achieved even by biomolecules. Therefore, the present study focuses on the flash flow synthesis

to achieve “living monoaddition” process for preparation of sequential oligomers by the reasons as depicted below.

Living radical polymerization methods typically employ mild reaction conditions and are easily applied to block copolymerization by using different monomers.[4] At the same time, the living radical process depends on controlling the equilibrium between the active radical species and the dormant species to suppress radical chain propagation and allow the regeneration of metastable dormant species.[5] Therefore, the living radical monoaddition process can only be achieved using monomers that differ greatly in thermodynamic stability, and thus, reactivity (Scheme 1a).[6] Meanwhile, anionic polymerization reactions initiated by organolithium species are irreversible and fast, and proceed without dormant species. Therefore, they represent a promising living monoaddition method for constructing sequence-defined oligomeric products. However, the current technology depends on the slow mixing under the reaction conditions of batch reactors, and therefore prevents the sequential anionic addition of various monomers.

Recently, the author has developed a flash living anionic polymerization that enables fast and selective reactions utilizing millisecond-order reactivity in polar solvents (Scheme 1b).[7,8] The flash microflow method enables the separation of reaction space into individual propagation steps via the fast diffusion of mass and heat in microscale quantities.[9,10] Hence, this method yielded polymers with almost ideal polydispersity and divergent block copolymerization with functional group tolerance. However, known strategies for single unit monomer insertion in living anionic polymerization are limited to the initiation and termination moieties because anionic living monoaddition under standard reaction conditions was fundamentally difficult. Once the author achieves sequential propagation of various monomers without undesired reactions with the flash microflow method, such living monoaddition process will be independent of the monomer reactivity and enables the divergent formation of sequence-defined oligomers (Scheme 1c).[11,12] Herein, a fast-flow, streamlined, and sequential monoaddition process is reported for alkenes with the orthogonal insertion of various functionalized monomers and end capping moieties, thus providing a sequence-defined method that enables the construction of novel molecules. Each monomer sequence can be introduced as a unimolecular unit or as an oligomeric unit with a specific chain length.

a)

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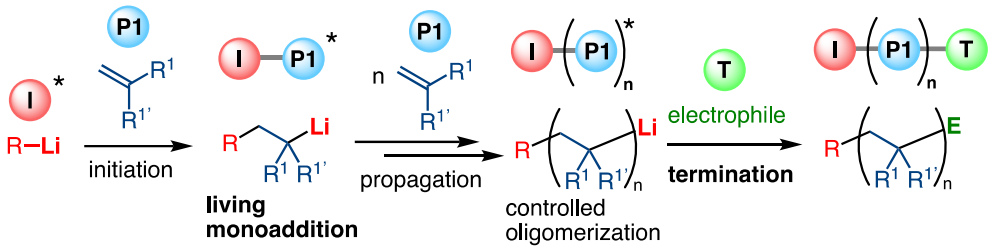


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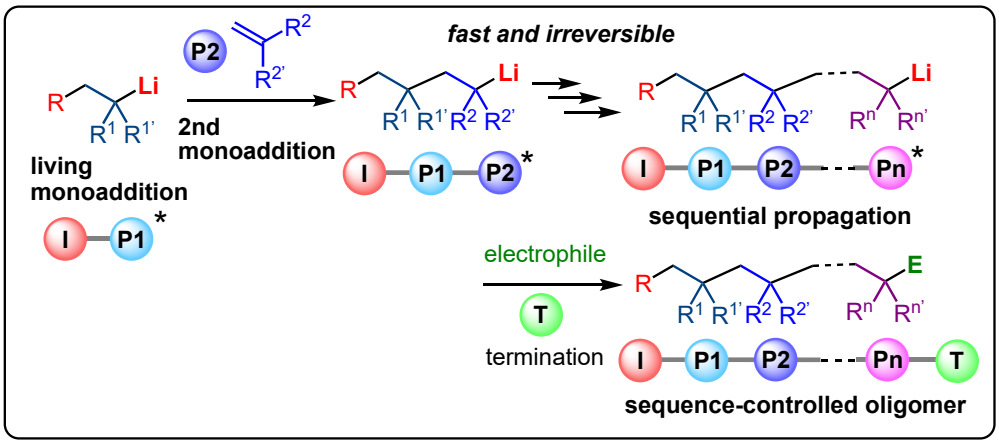
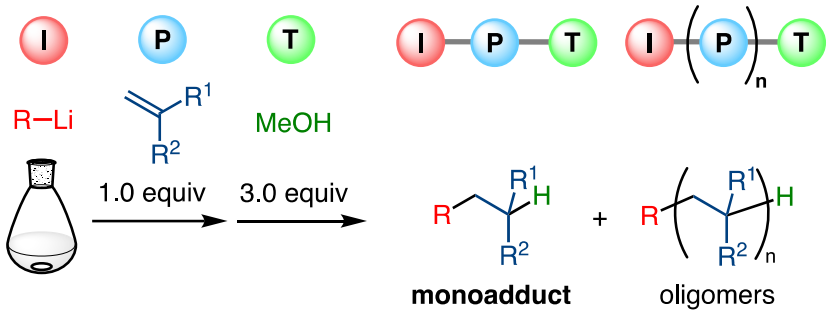



**Scheme 1.** Approaches to the synthesis of sequence-defined linear molecules. a) Living radical monoaddition of alkenes. a) Living radical monoaddition of alkenes. b) Flash living anionic polymerization. c) Flash living anionic monoaddition of polymerizable alkenes (present work).

## 2-2. Results and discussion

a)

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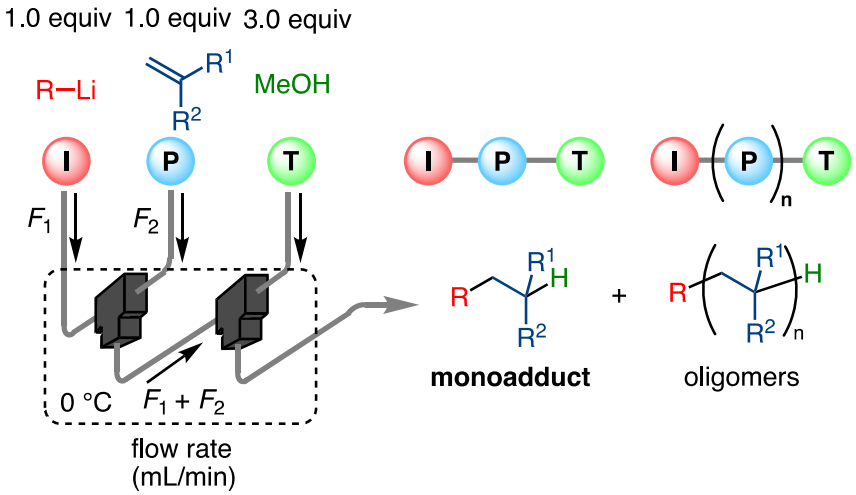


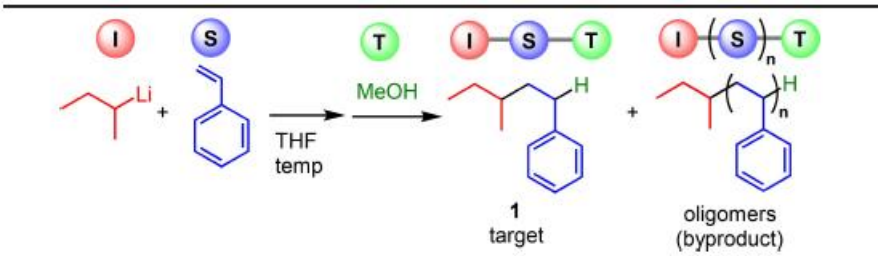

**Scheme 2**. Attempt for monoaddition of styrene to an alkyllithium reagent. a) Slow addition method using a batch reactor. b) Flash addition method using a flow microreactor.

Initial attempt to achieve a 1 :1 monoaddition sequence began with the addition of sec-butyllithium (*s*-BuLi) to styrene using batch-type reaction vessels (Scheme 2a). An excess amount of *s*-BuLi solution in hexane was added dropwise within 5 min to a styrene solution in THF. After methanol was added to terminate the reaction, the full consumption of starting styrene was observed. Using this method yielded a mixture of oligomers and a low percentage of the target 1: 1 addition product **1**. These results were consistent at different temperatures, ranging from 0 to –78 °C (Table 1a, entries 1–4). These data indicated that the selective generation of the 1: 1 addition product was unachievable under the typical reaction conditions (i.e., vessel size and reaction time and temperature).

Therefore, the author hypothesized that the use of a flash flow method could ensure rapid mixing around the millisecond order time and complete reaction within the sub-second order, enabling

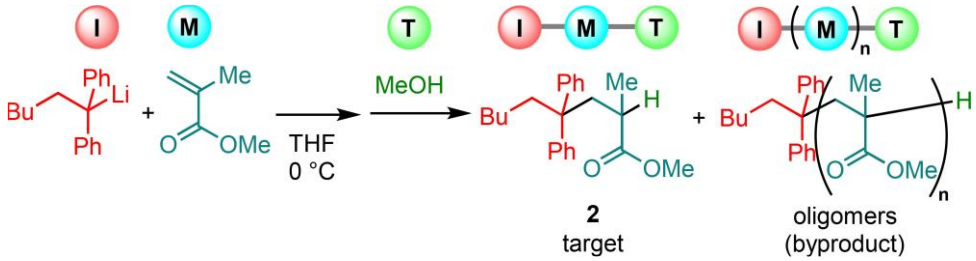
highly selective 1 :1 addition of alkyllithium and styrene. Thus, the author set up a microflow reactor equipped with a T-shaped mixer for the rapid reaction of *s*-BuLi and styrene, followed by a second mixer to terminate the reaction with MeOH (Scheme 2b). The reaction with a normal flow rate of 1.5 mL/min afforded the monoaddition product **1** preferentially, albeit in a very low yield (Table 1a, entry 5). Then the author tested higher flow rates (3.0–18 mL/min) with the same system, and the selectivity for the monoaddition product **1** dramatically improved (Table 1a, entries 6–10). At a flow rate of 15 mL/min, the highest yield for **1** (93%) was obtained, with only 2% byproducts ($n$ = 2) and trace amounts of larger oligomers. The styrene monomer was fully consumed in all the experiments varying flow rates. The reaction rate in the anionic initiation of alkyllithium species towards vinyl monomers will be much faster than the current range of residence time (0.50–7.9 sec) in these experiments. Therefore, the mixing efficiency derived from the rapid mixing is considered as a key factor for the selectivity. The oligomer formation profile was obtained via gel permeation chromatography (GPC) analysis (Figure 1). The products from the batch-vessel reaction showed a large dispersion of formation ratios, whereas the products from the fast microflow reaction showed considerably less.

**Table 1.** The impact of high-flow-rate flash synthesis on yield compared to batch or normal flow methods.




a) St (styrene)

| Entry | Method | Temp (°C) | Flow rate $F_1+F_2$ (mL/min) | Yield (%) | | |
|---|---|---|---|---|---|---|
| | | | | **1** | Oligomer ($n=2$) | Oligomer ($n=3$) |
| 1 | batch | 0 | – | 8 | 5 | 9 |
| 2 | batch | −20 | – | 8 | 5 | 9 |
| 3 | batch | −50 | – | 8 | 5 | 9 |
| 4 | batch | −78 | – | 8 | 5 | 9 |
| 5 | flow | 0 | 1.5 | 20 | trace | 3 |
| 6 | flow | 0 | 3.0 | 66 | 8 | 4 |
| 7 | flow | 0 | 6.0 | 88 | 5 | 1 |
| 8 | flow | 0 | 12 | 90 | 2 | trace |
| 9 | flow | 0 | 15 | 93 | 2 | trace |
| 10 | flow | 0 | 18 | 90 | 2 | trace |




b) MMA (methyl methacrylate)

| Entry | Method | Flow rate F1 + F2 (mL/min) | Yield (%) | |
|---|---|---|---|---|
| | | | **2** | Oligomer ($n = 2$) |
| 1 | batch | – | 43 | – |
| 2 | flow | 1.5 | 34 | 7 |
| 3 | flow | 2.0 | 43 | 12 |
| 4 | flow | 4.0 | 78 | 13 |
| 5 | flow | 8.0 | 86 | 9 |
| 6 | flow | 16 | 87 | 9 |
| 7 | flow | 24 | 89 | 9 |

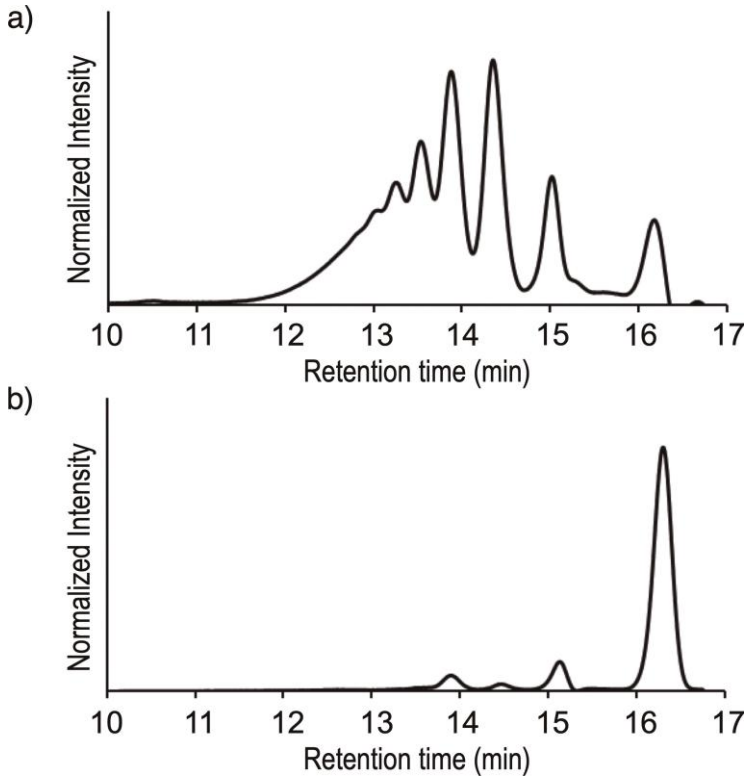
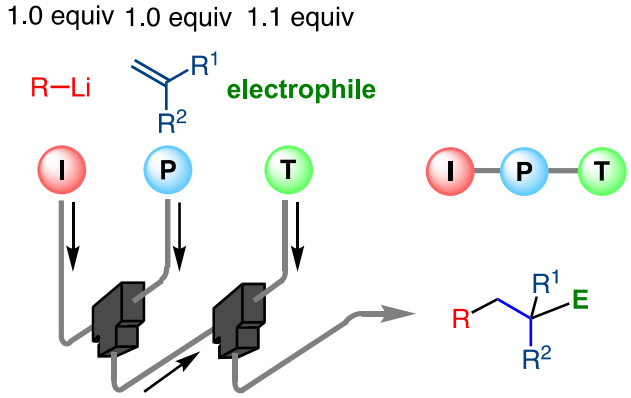



**Figure 1.** GPC curves for investigations of styrene monoaddition in a) batch and b) flow reaction. The peak of target product **1** was detected at 16.2 min. Oligomers were detected at 15.0 min ($n$ = 2), 14.2 min ($n$ = 3), and fewer retention times. The yields of the oligomers were estimated by calibrating the GPC peak area by Gaussian fitting.

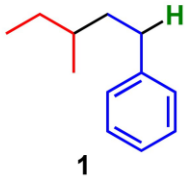
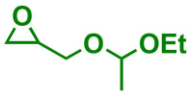
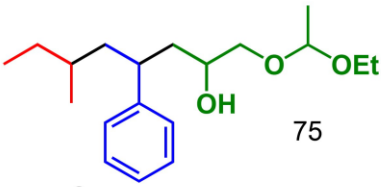
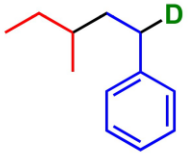
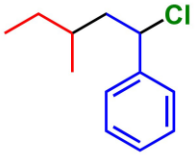
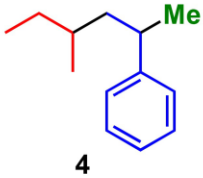
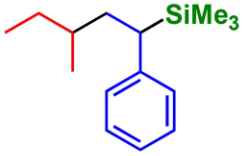
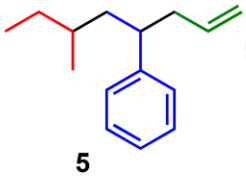
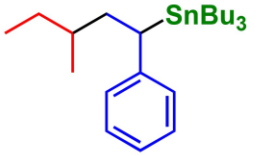
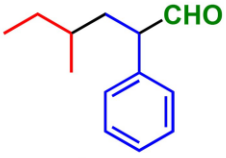
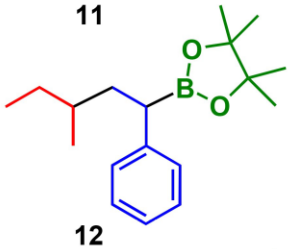
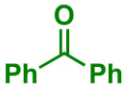
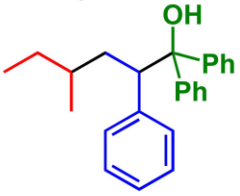
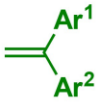
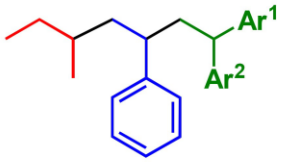
The author also attempted a methacrylate monomer as another type of vinyl monomers using the same system.[8] The author examined the anionic addition of *n*-butyllithium to 1,1-diphenylethylene to form DPHLi (1,1-diphenylhexyllithium) as a milder alkyllithium initiator (Table 1b). 1,1-Diphenylalkyllithium species are known to initiate the anionic polymerization of methacrylates efficiently. Less bulky and/or more reactive alkyllithium species such as *s*-BuLi undergoes the 1,2-addition to the ester moieties besides the 1,4-addition. Actually, DPHLi triggered the living addition of methyl methacrylate followed by protonation with methanol. While the yield of the target 1: 1 adduct 2 was only 43% under batch conditions (entry 1), using the flash flow system with an increased flow rate (24 mL/min) dramatically increased the yield to 89% (entries 2–7). These results show that this flow monoaddition method can be used with several vinyl monomers that are commonly used in living anionic polymerization.




**Scheme 3.** Selective three-component coupling sequence by using a microflow system.

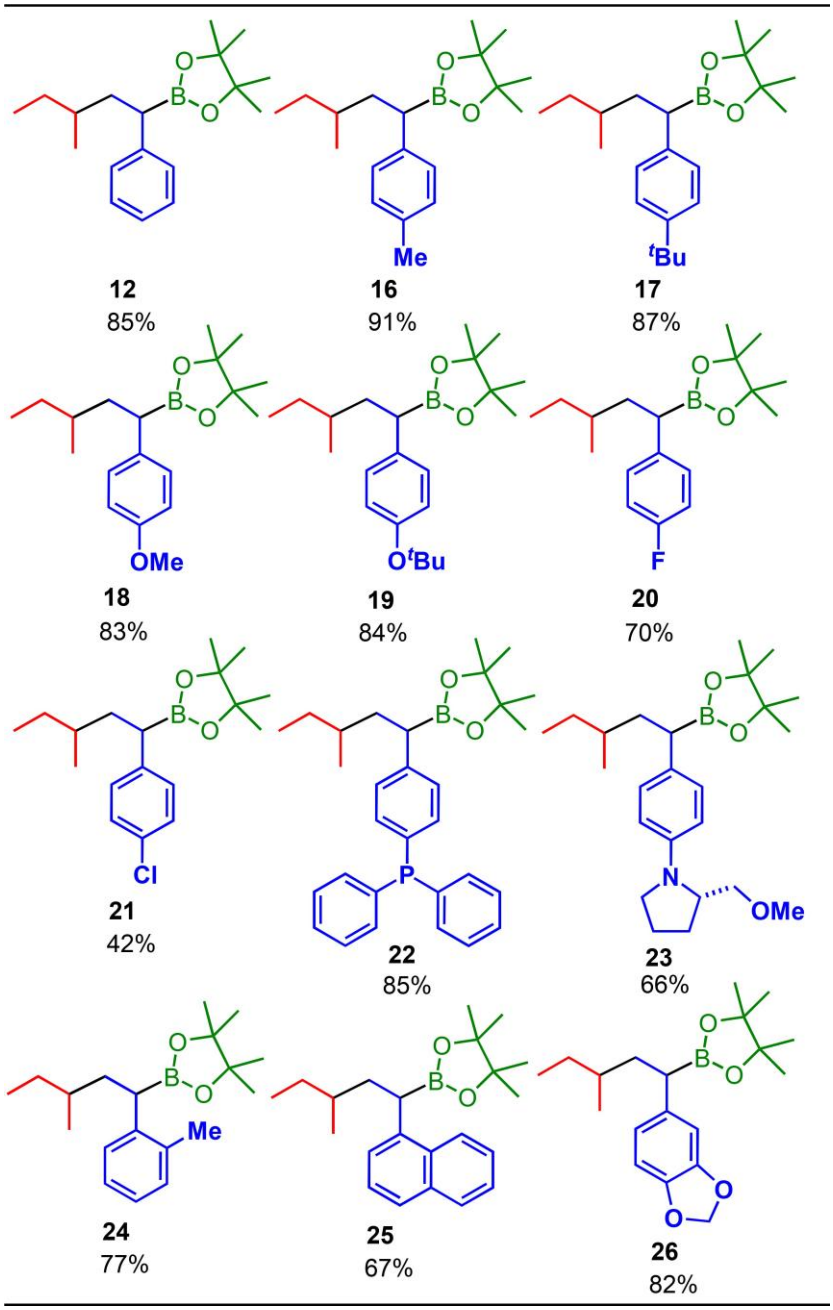
With the optimized flow conditions in hand, the author concentrated on end-capping of the dormant species on the living terminus (Scheme 3). This is one of the most important strategies for polymer synthesis because it allows terminal modifications in functional polymers. However, the monoaddition sequence of polymerizable monomers often has many limited capping reagents because of the differences in the kinetic rates of the capping reactions. In this method, the author successfully introduced a variety of electrophilic reagents into the living terminus of the 1: 1 adduct of *s*-BuLi and styrene (Table 2). Using a deuterated quencher $CD_3OD$ resulted in monodeuterated product **3** in high yield and a high deuterium incorporation ratio. Alkylative terminal modifications were also achieved by trapping the intermediate with MeI and allyl iodide in good to excellent yields (**4** and **5**). Reactions of the carbonyl moieties with DMF and benzophenone produced the corresponding aldehyde **6** and tertiary alcohol **7**, respectively. Similar electrophilic trapping with an epoxide reagent afforded the ring-opening product alcohol **8** in high yield, suppressing further oligomerization with the epoxide reagent. Halogenation of the organolithium terminus also proceeded smoothly to give 84% yield of chlorinated 1:1 adduct **9**, which could undergo further functionalization. It has been previously reported by the author that the direct metalation of organolithium active species in flash flow systems with various metal sources, such as stannane and boron reagents, which can readily be used in cross-coupling processes.[9] Silylation, stannylation, and borylation with chlorinated or alkoxylated reagents were all successful in affording the corresponding organometallic products **10**–**12** in high yields. Finally, addition of other alkene derivatives to the living terminus afforded diarylalkane moieties **13**–**15** with or without halogen functional groups, in high yields.[13] Overall, these results demonstrate the diversity of the series of sequential additions with anionic initiators, styrene, and electrophilic reagents in a 1: 1: 1 ratio.

**Table 2.** Selective three-component coupling sequence involving the monoalkylation of styrene followed by trapping with various electrophilic reagents.

| electrophile | product | yield (%)[a] | electrophile | product | yield (%)[a] |
|---|---|---|---|---|---|
| MeOH |  **1** | 84 |  |  **8** | 75 |
| $CD_3OD$ |  **3** | 87 | $CCl_4$ |  **9** | 84 |
| MeI |  **4** | 84 | $ClSiMe_3$ |  **10** | 86 |
|  |  **5** | 96 | $ClSnBu_3$ |  **11** | 79 |
| DMF[b] |  **6** | 88 | *i*PrOBpin |  **12** | 85 |
|  |  **7** | 49 |  |  | |
| | | | | **13** ($Ar^1$ = $Ar^2$ = Ph) | 81 |
| | | | | **14** ($Ar^1$ = $Ar^2$ = 4-$ClC_6H_4$) | 80 |
| | | | | **15** ($Ar^1$ = 4-$BrC_6H_4$, $Ar^2$ = Ph) | 85 |

[a] GC yield. [b] Stirred at rt for 30 min before the reaction was quenched with 1 N HCl aq.

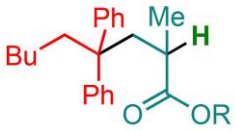
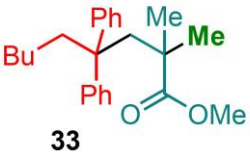
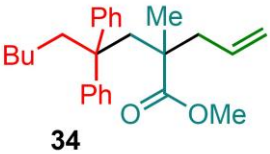
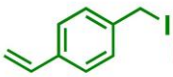
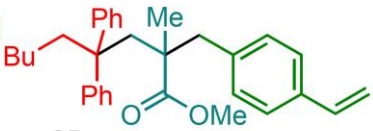
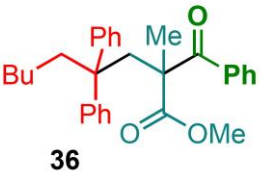
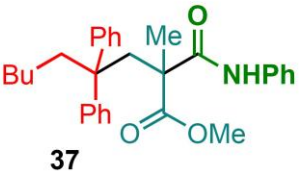
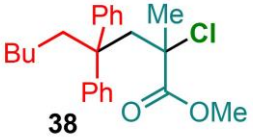
**Table 3**. Monoaddition of variously functionalized styrenes into three-component coupling sequence.



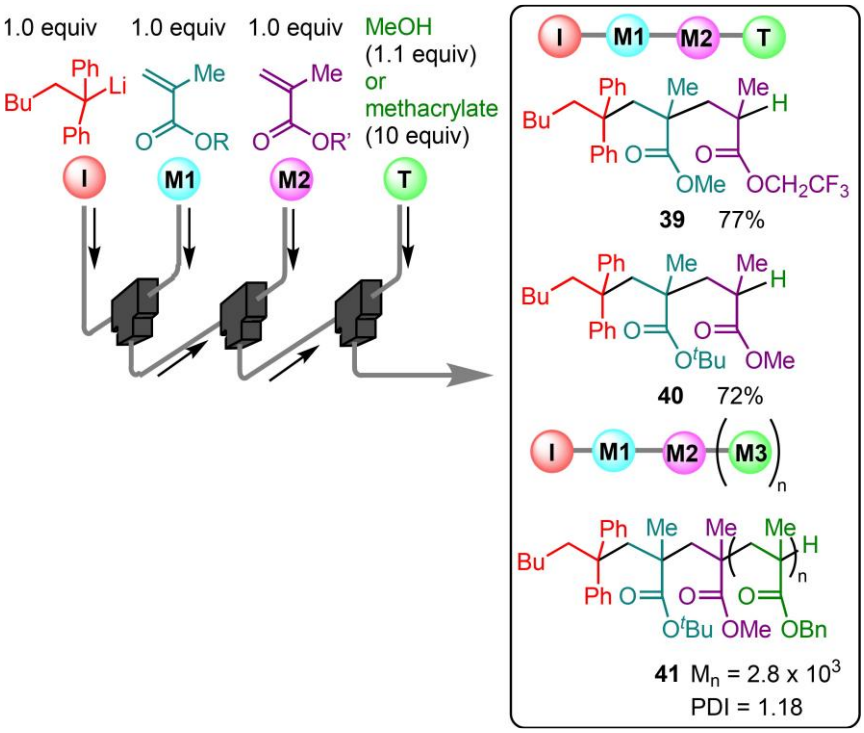
The use of functionalized styrene monomers could present a problem for selective monoaddition because of the differences in the kinetic reactivities of these monomers.[14] This fast-flow synthetic method overcame these limitations and successfully worked well with various functionalized styrene derivatives for three-component sequential addition reactions (Table 3). The incorporation of alkylated or alkoxylated styrenes into the sequence, followed by borylative termination with $^{i}$PrOBpin, successfully afforded the *para*-alkylated or -alkoxylated products **16**–**19** in high yields. Styrene monomers containing halogen substituents attached to the aromatic ring were tolerated and gave the corresponding products **20** and **21** in good and acceptable yields, respectively, despite the risk of side reaction by halogen-lithium exchange. Actually, byproducts derived from halogen-lithium exchange were not observed. The majority of the byproducts was the oligomeric products including a multiple chloro-styrene unit. Monomers bearing heteroatomic substituents, such as phosphine [15] and chiral amine moieties,[16] were also incorporated into the sequence without decomposition of the substituents (**22** and **23**). Bulkier styrene analogs, such as o-methylstyrene and 1-vinylnaphthalene, successfully afforded the corresponding 1:1:1 sequence in good yield without decreasing selectivity (**24** and **25**). Methylenedioxyphenyl moieties, which are precursors of catechol, were tolerated under these conditions to give compound **26** in 82% yield.

Living oligomerization of methacrylate esters gives lithium enolates as living termini, which shows nucleophilicity lower than those of styrene derivatives. This delays the termination of the living monoaddition. The present functionalization method with a high-flow-rate flash system enabled the selective formation of three-component adducts with various electrophiles (Table 4). Although the general reactivity of methacrylate esters for anionic polymerization strongly depends on the substituents, this approach successfully led to mono-selective termination by protonation without impairing the type of alkylated methacrylates used (**27**–**32**). The scope of terminal alkylation is broadened to include methylation, allylation, and benzylation as third components (**33**–**35**). In particular, for benzylation, a styrene unit was introduced into the terminus of product **35**, which can further elongate the polymer chains with the sequence defined oligomer unit by using another vinyl polymerization. Termination with carbonyl compounds, including a carboxylic chloride and an isocyanate, proceeded efficiently to afford the corresponding ketone or amide in high yields (**36** and **37**). Halogen substituents are also useful for further functionalization of the sequence-defined oligomer products, and the same approach was applied to the terminal chlorination to form α-chloroester **38** in 86% yield by using carbon tetrachloride as a chlorination reagent.

**Table 4**. Electrophilic trapping of reactive lithium enolate intermediate

| electrophile | product | yield (%)[a] |
|---|---|---|
| MeOH |  | |
| | **2** (R = Me) | 90 |
| | **27** (R = Et) | 82 |
| | **28** (R = Bu) | 80 |
| | **29** (R = $^{i}$Pr) | 66 |
| | **30** (R = $^{t}$Bu) | 97 |
| | **31** (R = Bn) | 76 |
| | **32** (R = $CH_2CF_3$) | 77 |
| MeI |  **33** | 87 |
|  |  **34** | 79 |
|  |  **35** | 87 |
| PhCOCl |  **36** | 83 |
| PhNCO |  **37** | 93[b] |
| $CCl_4$ |  **38** | 86 |

[a] GC yield. [b] Stirred at rt for 15 min after the flow reaction.



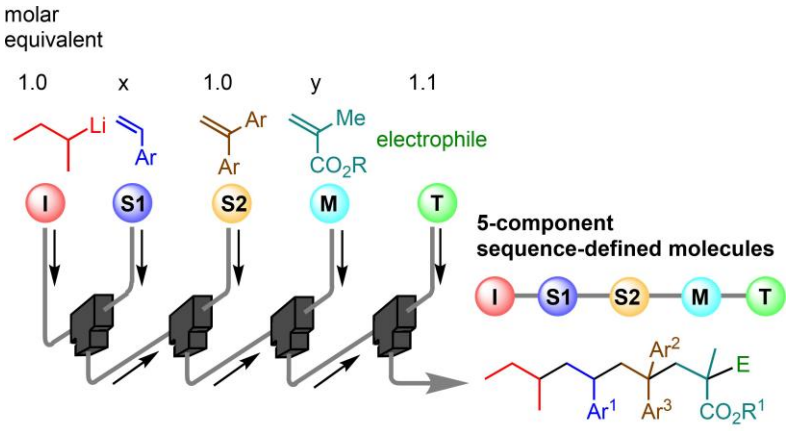

**Scheme 4**. Four-component coupling sequence derived from two different methacrylate monomers.

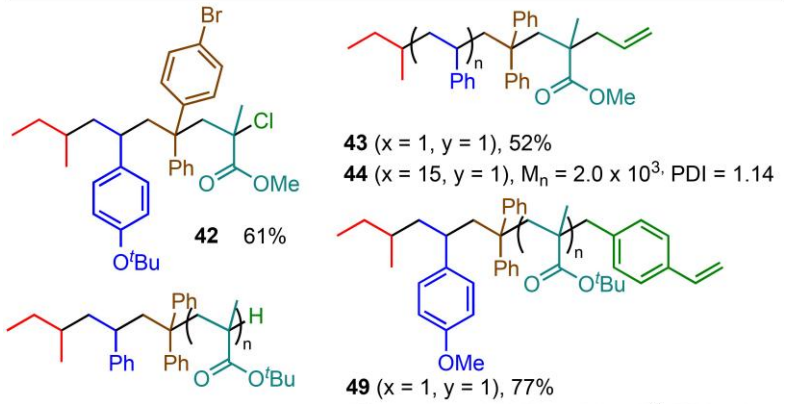
The most important feature of the present sequence construction method is the introduction of different vinyl units in a one-to-one correspondence using the polymerizability of living termini, which enables the preparation of linear sequences by arranging various units possessing divergent stereochemical or physical properties. As depicted in Scheme 4, an influx of the organolithium initiator was followed by two different alkyl methacrylates **M1** and **M2** and finally terminated with methanolic protonolysis to form the corresponding four-component sequence-defined molecules in good yields (**39** and **40**). An excess amount of the third methacrylate monomer solution was then delivered to the final channel instead of the MeOH solution to construct the partially sequence-defined oligomer **41**. As a result, the first two monomers were introduced in a mono-selective manner and the third monomer was introduced as an oligomer with a chain length corresponding to the molar amount. These findings provide valuable insights into polymerization technologies that bear sequence-defined units.

The result that the oligomer units were selectively introduced into the sequence-defined molecule encouraged the author to attempt it with oligomer units of any chain length. Prior to these attempts, the author examined the synthesis of five component products with one-to-one correspondence, both bearing styrene and methacrylate monomers. The living terminus of the styrene monoadduct (**I-S1***) was reacted with a diphenylethylene spacer unit (**S2**) followed by a

second monoaddition with a methacrylate monomer (**M**) and finally terminated with a termination reagent (**T**) to give 61% yield of the corresponding five-component molecule **42** with various functionalized moieties like ether, bromoarene, chloroalkane, and ester moieties (Table 5). The reactions of similar combinations of functionalized components also afforded the five-component products **43**, **45**, and **49** in good yields and with high selectivity.

**Table 5**. Five-component coupling sequence composed of alkyllithium, one or multiple molecules of styrenes, diarylethylenes, one or multiple molecules of methacrylates, and electrophilic reagents.



**42** 61%

**43** (x = 1, y = 1), 52%

**44** (x = 15, y = 1), $M_n$ = 2.0 x $10^3$, PDI = 1.14

**45** (x = 1, y = 1), 74%

**46** (x = 1, y = 4) and **47** (x = 1, y = 7), unimodal oligomers

**48** (x = 1, y = 13), $M_n$ = 2.5 x $10^3$, PDI = 1.16

**49** (x = 1, y = 1), 77%

**50** (x = 1, y = 10), $M_n$ = 2.0 x $10^3$, PDI = 1.15

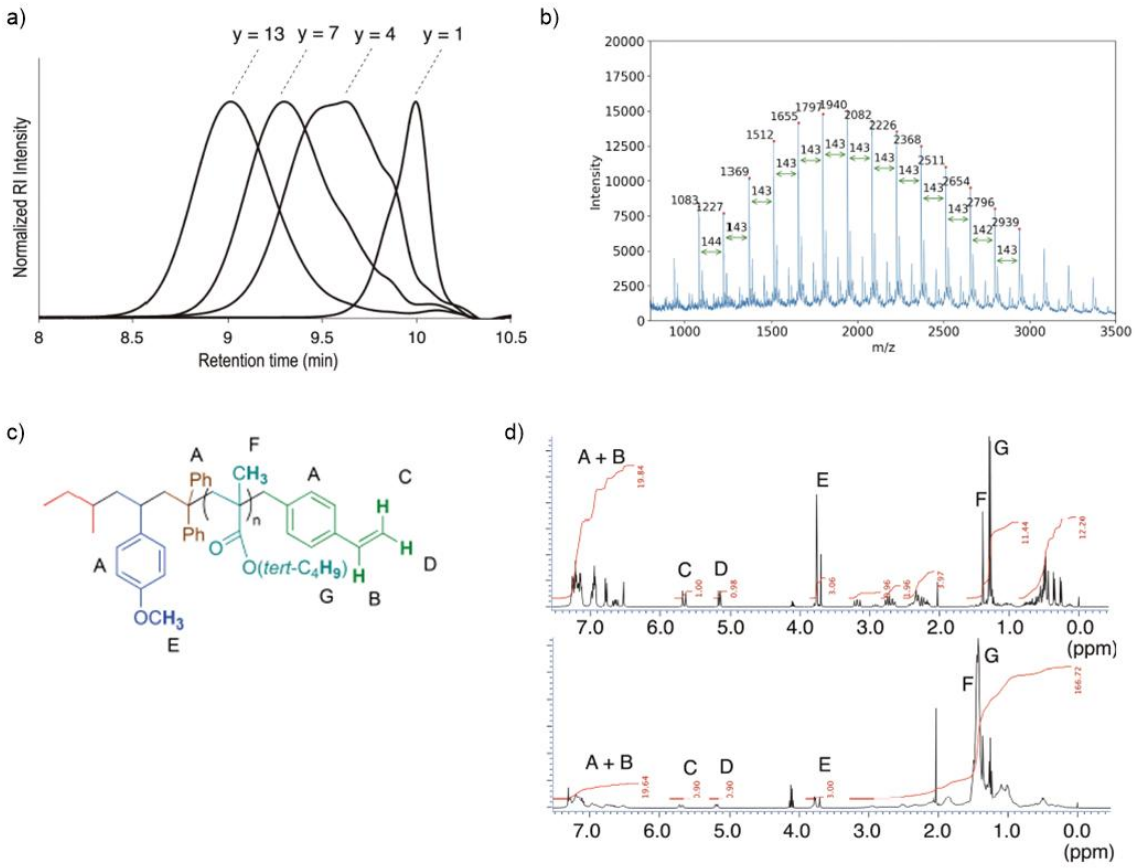
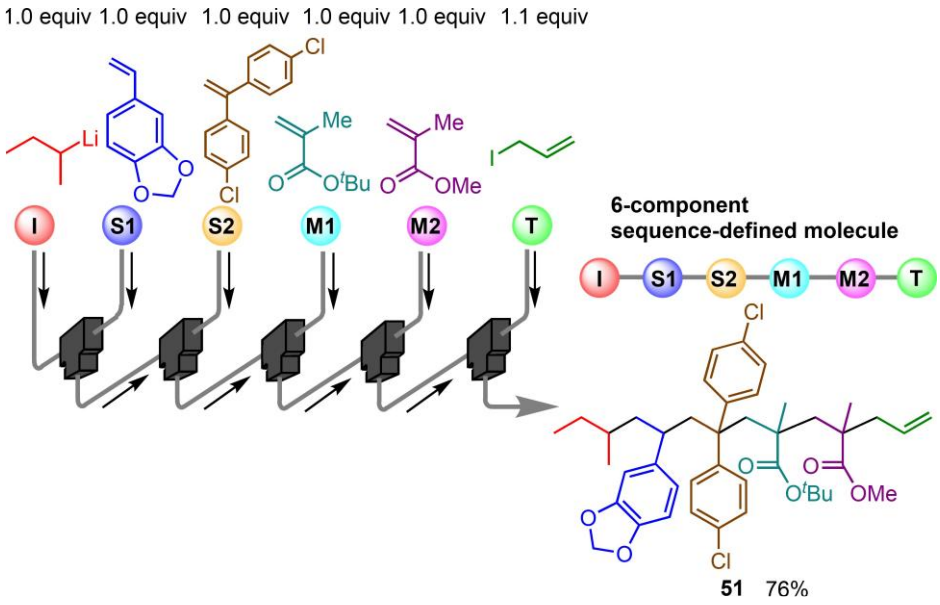



**Figure 2**. Spectral data for insertion of the oligomeric unit into the unimolecular sequences. a) GPC curves for **45**–**48**. b) MALDI-MS spectrum of oligomer **48**, in which the peak top at m/z = 1940 in accordance with GPC analysis and the mean peak interval is 142 in accordance with the monomeric unit *t*-BuMA. c) Assignment for $^{1}$H NMR spectra of sequential product **49** and the corresponding methacrylate oligomer **50** in $CDCl_3$. The number of methacrylate units (~9.5) calculated by $^{1}$H NMR spectroscopy agrees with the degree of polymerization (~9.1) estimated by GPC analysis.

Once the author obtained **45**, the equivalents of the methacrylate monomer were varied (1, 4, 7, and 13 equivalents). GPC analysis of the oligomers obtained demonstrated a shift in the molecular weight distribution proportional with an increase in equivalents of methacrylate (Figure 2a). It also revealed low dispersion of formation ratio, which was supported by MALDI-MS results (Figure 2b). The author attempted a second modification by changing the amount of styrene unit **S1** from 1 to 15 equivalents. The author obtained styrene oligomer **46**–**48** without varying the other one-to-one sequence units, as confirmed by $^{1}$H NMR analysis (Figure 2c, *see* also Supporting Information). Additionally, 10 equivalents of the methacrylate monomer **M** were

successfully introduced into the internal position of the sequence-defined molecules to obtain oligomer **50** with good molecular weight control and a low dispersion of formation ratio. These findings suggest that the chain length of the oligomer unit for the sequence-defined products can be altered simply by modifying the monomer equivalents without affecting the sequence control of the other units.

The number of sequence-defined units in the present living monoaddition method reached a maximum of six in with the following sequence: initiator **I**, styrenes **S1** and **S2**, methacrylates **M1** and **M2**, and terminating electrophile **T**. In only 13.4 s of total residence time, the six-component reaction product **51** with a molecular mass of 736 was obtained in 76% yield (Scheme 5). Although the present technical achievement using flash microflow system was the sequence-defined oligomers less than 1,000 molecular weight, this methodology provides immeasurable prospects for future synthetic methods for completely sequence-defined oligomers.




**Scheme 5**. Six-component coupling sequence composed of alkyllithium, styrenes, diarylethylenes, two different methacrylates, and electrophilic reagents.

## 2-3. Conclusion

The author has developed a living monoaddition of polymerizable vinyl monomers, including styrenes and methacrylates, via flash flow technology that allowed optimal mixing conditions. Sequence-defined molecules with up to six components, including initiators, various monomers, and terminating electrophiles, were obtained in good yield with high selectivity. The substrates used in this study exhibit a theoretically accessible combination of six-component products, reaching 1×12×3×7×7×7=12348. Notably, fully synthetic sequence-defined molecules with nearly infinite combinations in were synthesized rapidly and selectively via existing synthetic methods on the conventional space/time scale. Taking advantage of the fast and selective living monoaddition over a very short time range, monomers were inserted inside the sequence as oligomers with the desired chain length, which indicates that the present sequence construction methodology is not limited to low-molecular-weight oligomers but can be expanded into functional polymers with fully sequence-defined domains. The present method provides a breakthrough sequence-defined synthesis that is less dependent on monomer reactivity and has the potential to allow the synthesis macromolecules with functions comparable to those of biomolecules.

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## 2-5. Experimental Section

### 2-5-1. General Information

**Abbreviations.** residence time of microtube reactor R*n* ($t^{Rn}$), and inner diameter of tubes and mixers ($\varphi$).

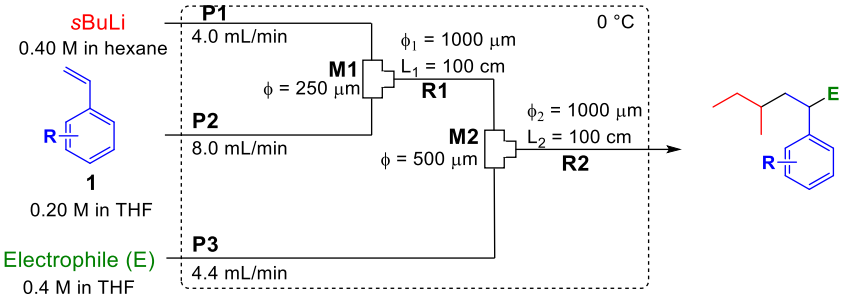
**General**. $^{1}$H and $^{13}$C NMR spectra were recorded on a JEOL ECZ-400S spectrometer ($^{1}$H 400 MHz, $^{13}$C 100 MHz). Chemical shifts are recorded using $Me_4Si$ (0.0 ppm) signals as an internal standard for $^{1}$H NMR, and methine signal of $CHCl_3$ for $^{13}$C NMR (77.0 ppm) unless otherwise noted. NMR yields were calculated by $^{1}$H NMR analyses using 1,1,2,2-tetrachloroethane (TCE) as an internal standard. GC analyses were performed on a SHIMADZU GC-2025 gas chromatograph equipped with a flame ionization detector using a fused silica capillary column (column, Rtx- 200; 0.25 mm × 30 m). GC yields were calculated by GC analyses with n-dodecane as an internal standard using calibration lines derived from commercial or isolated compounds with the internal standards. GC-MS analysis was performed on a SHIMADZU GCMS-QP2020 NX. GPC analysis was performed on a SHIMADZU CTO-20A with a Shodex RI-504 RI detector. GPC yields were calculated by GPC analyses using Gaussian Fitting by OriginPro 8.1J SR1 analysis software. Mass spectra were recorded on Thermo Fisher Scientific EXACTIVE plus (ESI and APCI) and JEOL JMS-700 (EI) in Instrumental Analysis Div., Global Facility Center, Creative Research Institution, Hokkaido University. MALDI-TOF-MS spectra were recorded on BRUKER microflex LRF in Toho Chemical Industry Co., Ltd. Merck pre-coated silica gel F254 plates (thickness 0.25 mm) were used for TLC analyses. Preparative GPC separation was performed on a JAI HPLC 9021 equipped with JAIGEL-1H and -2H columns. All batch reactions were carried out in a flame-dried glassware under argon atmosphere unless otherwise noted.

**Flow Synthesis.** Stainless steel (SUS304) T-shaped micromixers with inner diameter of 500 μm and 250 μm were manufactured by Sanko Seiki Co., Inc. Stainless steel (SUS316) microtube reactors with 1000 μm inner diameter and PTFE tubes with inner diameter of 1000 μm were purchased from GL Sciences. The syringe pumps (Harvard PHD ULTRA) equipped with gastight syringes (SGE 50MR-LL-GT or 100MR-LL-GT) were used for introduction of the solutions into the micromixer systems *via* stainless steel fittings (GL Sciences, 1/16 OUW). Flow microreactor system is composed with stainless steel pre-cooling units (**P1**, **P2**, etc.), stainless steel microtube reactors (**R1**, **R2**, etc.), T-shaped micromixers (**M1**, **M2**, etc.), and, if necessary, PTFE tube with inner diameter of 1000 μm. The solution of *n*-butyllithium and *sec*-butyllithium was prepared by dilution of those commercial solution with dehydrated *n*-hexane.

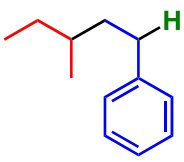
**Materials**. Dry THF and n-hexane were purchased from Kanto Chemical Co., Inc., and were used after passing through the purification column in the solvent dispenser system. Solutions of n-butyllithium and sec-butyllithium were purchased from Kanto Chemical Co., Inc. and stored at −20 °C. Styrene monomers, methacrylate monomers, and 1,1-diphenylethylene, were purchased from commercial suppliers, and used after vacuum distillation. 1,1- Diphenylhexyllithium **6** and

4-vinylbenzyl iodide **7** were prepared according to the reported procedure.

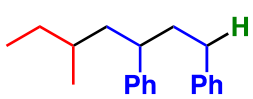
### 2-5-2. Synthesis of Styrene Monoaddition product in a Flow Microreactor.




A flow microreactor system consisting of two T-shaped micromixers (**M1** and **M2**), two microtube reactors (**R1** and **R2**), and three pre-cooling units (**P1** (L = 100 cm), **P2** (100 cm) and **P3** (100 cm)) was used in a cooling bath at 0 °C. A solution of *s*-BuLi (0.40 M in hexane, flow rate: 4.0 mL/min) and a solution of styrene's analog (**1**, 0.20 M in THF, flow rate: 8.0 mL/min) were introduced to **M1** ($\phi$ = 250 μm) using syringe pumps, and the mixture was passed through **R1** (100 cm, residence time $t^{R1}$ = 3.9 s). The resulting solution was introduced to **M2** ($\phi$ = 500 μm), where a solution of electrophile (0.4 M in THF) was also introduced (flow rate: 4.4 mL/min). The resulting solution was passed through **R2** ($\phi$ = 1000 μm, L = 100 cm, residence time = 2.9 s). After a steady state was reached, the product solution was collected for 30 seconds. To the aliquot, sat. $NH_4Cl$ aq. was added, and then the organic phase was analyzed by GC.




**(3-methylpentyl)benzene:** Obtained from styrene and $CH_3OH$ as the styrene's analog and electrophile in 84% yield (GC yield). Yields were determined by GC analysis using an internal standard ($C_{12}H_{26}$). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 57% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.15-7.31 (m, 5H), 2.52-2.68 (m, 2H), 1.59-1.68 (m, 1H), 1.47-1.35 (m, 3H), 1.19 (qd, *J* = 6.4, 7.6 Hz, 1H), 0.92 (d, *J* = 6.4 Hz, 3H), 0.87 (t, *J* = 7.2 Hz, 3H); $^{13}$C NMR (100MHz, $CDCl_3$) δ 143.3, 128.5, 128.4, 125.6, 38.7, 34.2, 33.6, 29.5, 19.2, 11.4. HRMS (EI) *m/z* Calcd for $C_{12}H_{18}$ $[M]^+$ 162.1409; Found: 162.1403.




**(3-methylpentyl)benzene:** Obtained from styrene and $CH_3OH$ as the styrene monomer and electrophile in 7% yield (GC yield) and mixture of two diastereomers. Yields were determined by GC analysis using an internal standard ($C_{12}H_{26}$). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 5% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$, diastereomer ratio = 50:50) δ 7.34-7.10 (m, 10H), 2.71-2.62 (m, 1H), 2.52-2.38 (m, 2H), 2.00-1.79 (m, 2H), 1.69 (ddd, *J* = 13.6, 10.4, 3.6 Hz, 0.50H), 1.60 (dt, *J* = 13.6, 7.2 Hz, 0.50H), 1.47-1.34 (m, 1.50H), 1.29-1.19 (m, 1H), 1.14-1.03 (m, 1.50H), 0.85-0.76 (m, 6H); $^{13}$C NMR (100MHz, $CDCl_3$, diastereomer ratio = 50:50) δ 146.2-145.7 (1C), 142.8 (1C), 128.4-128.3 (8C), 127.9-127.8 (1C),

126.0-125.7 (1C), 44.5-43.9 (1C), 43.1 (1C), 39.8-38.6 (1C), 34.0 (1C), 31.7 (1C), 30.4-28.8 (1C), 19.7-18.8 (1C), 11.3-11.1 (1C). HRMS (EI) *m/z* Calcd for $C_{20}H_{26}$ $[M]^+$ 266.2035; Found: 266.2034.

Figure S1 shows the GPC chart for the synthesis of styrene monoadduct. In the batch reaction, polymerization was not controlled and multiple polymer peaks appeared, whereas in the flow reaction, polymerization was controlled and only the monoadduct peak appeared significantly. Next, we examined the synthesis of oligomers by increasing the amount of styrene equivalent added by changing the concentration of styrene solution (Table S1). As a result, oligomers with controlled molecular weight distribution could be synthesized at each equivalent amount. In particular, oligomers with the lowest molecular weight dispersion (PDI) and high monodispersity were obtained at 15 equivalents. Figure S2 shows GPC charts for the addition of 1, 4, 8, and 15 equivalents of styrene. It was observed that the peak tops shifted to the polymer side with increasing styrene equivalent.

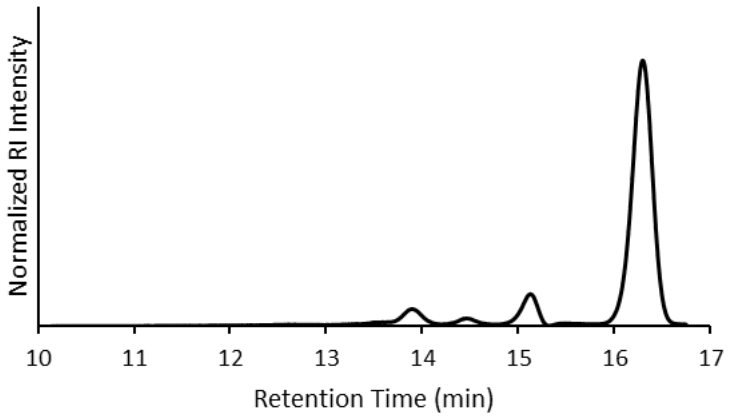
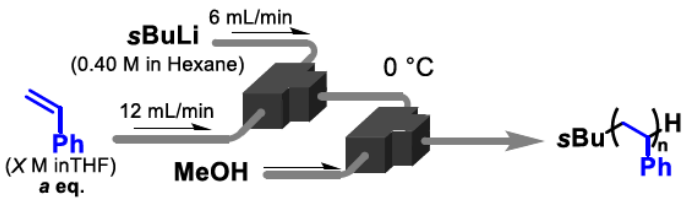



**Figure 3.** GPC chart for synthesis of styrene monoadduct.

**Table 6.** Oligomer synthesis by changing styrene equivalents.




| *a* (eq.) | *X* (M) | $M_n$ | PDI | Conv. (%) |
|---|---|---|---|---|
| **1** | 0.20 | 180 | **1.09** | 100 |
| **2** | 0.40 | 290 | **1.15** | 100 |
| **3** | 0.60 | 370 | **1.14** | 100 |
| **4** | 0.80 | 460 | **1.13** | 100 |
| **5** | 1.0 | 630 | **1.12** | 100 |
| **6** | 1.2 | 740 | **1.12** | 100 |
| **7** | 1.4 | 850 | **1.11** | 100 |
| **8** | 1.6 | 980 | **1.10** | 100 |
| **9** | 1.8 | 1100 | **1.10** | 100 |
| **10** | 2.0 | 1100 | **1.10** | 100 |
| **15** | 3.0 | 1700 | **1.06** | 100 |

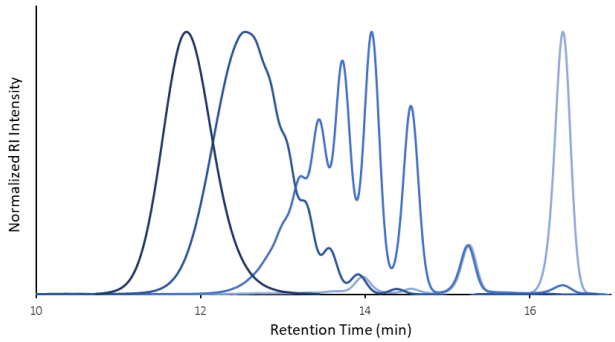
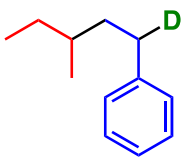
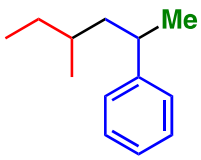


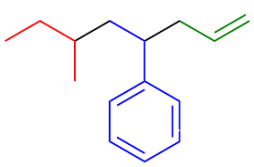

**Figure 4.** GPC chart for synthesis of styrene oligomers.



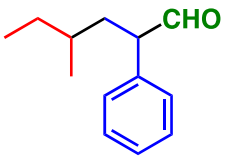

**(3-methylpentyl-1-d)benzene:** Obtained from styrene and $CD_3OD$ as the styrene's analog and electrophile in 85% yield (GC yield). Yields were determined by GC analysis using an internal standard ($C_{12}H_{26}$). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 55 % isolated yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.15-7.30(m, 5H), 2.52-2.67 (m, 1H), 1.59-1.68 (m, 1H), 1.47-1.34 (m, 3H), 1.19 (qd, $J$ = 6.4, 7.6 Hz, 1H), 0.92 (d, $J$ = 6.4 Hz, 3H), 0.87 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (100MHz, $CDCl_3$) δ 143.3, 128.5, 128.4, 125.7, 38.7, 34.2, 33.3 (t, $J$ = 19.1 Hz, 3H), 29.5, 19.3, 11.5. HRMS (EI) *m/z* Calcd for $C_{12}H_{17}D[M]^+$ 163.1471; Found: 163.1472.



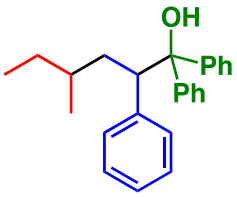

**(4-methylhexan-2-yl)benzene:** Obtained from styrene and MeI as the styrene monomer and electrophile in 84% yield (GC yield) and mixture of two diastereomers. Yields were determined by GC analysis using an internal standard ($C_{12}H_{26}$). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 67% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$, diastereomer ratio = 48:52) δ 7.30-7.15 (m, 5H), 2.84-2.75 (m, 1H), 1.65 (ddd, *J* = 13.6, 9.6, 4.4 Hz, 0.48H), 1.49 (ddd, *J* = 13.6, 7.6, 6.4 Hz, 0.52H), 1.43-1.24 (m, 2.52H), 1.22 (dd, *J* = 6.8, 3.6 Hz, 3H), 1.17-1.05 (m, 1.48H), 0.86-0.78 (m, 6H); $^{13}$C NMR (100MHz, $CDCl_3$, diastereomer ratio = 48:52) δ 148.6-147.9 (1C), 128.4 (2C), 127.2-127.1 (2C), 125.9 (1C), 45.9-45.5 (1C), 37.5-37.3 (1C), 32.0-31.9 (1C), 30.0-29.5 (1C), 23.6-22.2 (1C), 19.4-19.1 (1C), 11.3 (1C). HRMS (EI) *m/z* Calcd for $C_{13}H_{20}$ $[M]^+$ 176.1565; Found: 176.1566.



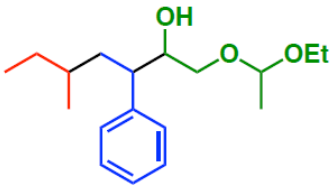
**(6-methyloct-1-en-4-yl)benzene:** Obtained from styrene and allyl bromide as the styrene monomer and electrophile in 96% yield (GC yield) and mixture of two diastereomers. Yields were determined by GC analysis using an internal standard ($C_{12}H_{26}$). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 36% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$, diastereomer mixture) δ 7.32-7.10 (m, 5H), 5.70-5.58 (m, 1H), 4.96-4.88 (m, 2H), 2.75-2.67 (m, 1H), 2.38-2.25 (m, 2H), 1.69-1.57 (m, 1H), 1.50-1.02 (m, 4H), 0.84-0.71 (m, 6H); $^{13}$C NMR (100MHz, $CDCl_3$, diastereomer mixtures) δ 145.9-145.4 (1C), 137.4-137.3 (1C), 128.4 (2C), 127.9-127.8 (2C), 126.0 (1C), 115.9-115.8 (1C), 43.5-43.0 (2C), 42.6-41.6 (1C), 31.7 (1C), 30.5-28.6 (1C), 11.9-18.8 (1C), 11.4-11.1 (1C). HRMS (EI) *m/z* Calcd for $C_{15}H_{22}$[M]+ 202.1716; Found: 202.1716.



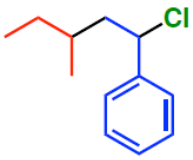

**4-Methyl-2-phenylhexanal:** Obtained from styrene and DMF as the styrene monomer and electrophile. After the product solution was collected and sat. HCl aq. was added to the aliquot, stirred this solution for 15 minutes. Yields were determined in 88% yield and mixture of two diastereomers by GC analysis using an internal standard ($C_{12}H_{26}$). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 56% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$, diastereomer ratio = 48:52) δ 9.68 (d, *J* = 2.4 Hz, 0.52H), 9.65 (d, *J* = 2.0 Hz, 0.48H), 7.40-7.19 (m, 5H), 3.64-3.59 (m, 1H), 2.09 (ddd, *J* = 6.8, 6.8, 13.6 Hz, 0.48 H), 1.87-1.75 (m, 1.04 H), 1.56 (ddd, *J* = 7.2, 7.2, 14.0 Hz, 0.48 H), 1.47-1.11 (m, 3H), 0.89-0.80 (m, 6H); $^{13}$C NMR (100MHz, $CDCl_3$, diastereomer ratio =48:52) δ 201.3-201.1 (1C), 136.9-136.5 (1C), 129.2 (2C), 129.0 (1C), 128.8 (1C), 127.6 (1C), 57.2-57.0 (1C), 36.7-36.2 (1C), 31.8-31.5 (1C), 30.0-28.9 (1C), 19.4-18.7 (1C), 11.3-11.1 (1C). HRMS (APCI) *m/z* Calcd for $C_{13}H_{19}O$ $[M+H]^+$ 191.1428; Found: 191.1430.



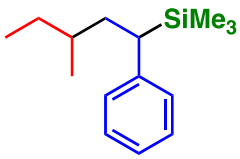

**4-Methyl-1,1,2-triphenylhexan-1-ol:** Obtained from styrene and benzophenone as the styrene monomer and electrophile in 49% yield (GC yield) and mixture of two diastereomers. Yields were determined by GC analysis using an internal standard ($C_{12}H_{26}$). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 23% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$, diastereomer ratio = 49:51) δ 7.61 (d, *J* =8.0 Hz, 2H), 7.38-6.98 (m, 13H), 3.90-2.84 (m, 1H), 2.44 (s, 1H), 2.01 (ddd, *J* = 13.2, 13.2, 2.8 Hz, 0.49H), 1.82 (ddd, *J* = 14.0, 12.0, 3.2 Hz, 0.51H), 1.60-1.49 (m, 1H), 1.38 (ddd, *J* = 12.8, 10.0, 2.0 Hz, 0.49 H), 1.19-0.85 (m, 2.51H), 0.90-0.68 (m, 6H); $^{13}$C NMR (100MHz, $CDCl_3$, diastereomer ratio = 49:51) δ 146.7-146.6 (2C), 146.1 (1C), 140.4-125.8 (15C), 81.2-81.1 (1C), 52.1-51.8 (1C), 37.1-36.5 (1C), 32.1 (1C), 31.0-27.5 (1C), 20.5-18.6 (1C), 11.6-11.0 (1C). HRMS (ESI) *m/z* Calcd for $C_{25}H_{28}ONa$ $[M+Na]^+$ 367.2032; Found: 367.2026.



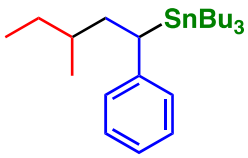

**1-(1-ethoxyethoxy)-6-methyl-4-phenyloctan-2-ol:** Obtained from styrene and EEGE (ethoxy ethyl glycidyl ether) as the styrene monomer and electrophile in 75% yield (GC yield) and mixture of two diastereomers. Yields were determined by GC analysis using an internal standard ($C_{12}H_{26}$). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$, diastereomer mixture) to give the product in 49% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.27-7.12 (m, 5H), 4.67-1.56 (m, 1H), 3.64-3.35 (m, 4H), 3.32-3.18 (m, 1H), 3.07-2.70 (m, 2H), 1.82-1.39 (m, 4H), 1.33-0.98 (m, 9H), 0.85-0.74 (m, 6H); $^{13}$C NMR (100MHz, $CDCl_3$, diastereomer mixture) δ 145.9-145.0 (1C), 128.5-128.4 (2C), 128.0-127.5 (2C), 126.1-126.0 (1C), 100.1-99.8 (1C), 70.6-69.1 (1C), 68.7-68.2 (1C), 61.1-61.0 (1C), 44.8-43.5 (1C), 41.5-40.4 (1C), 39.6-39.4 (1C), 31.7-31.5 (1C), 30.4-28.5 (1C), 19.8 (1C), 18.8-18.7 (1C), 15.2 (1C), 11.2-10.9 (1C). HRMS (ESI) *m/z* Calcd for $C_{19}H_{32}O_3Na$ $[M+Na]^+$ 331.2244; Found: 331.2234.



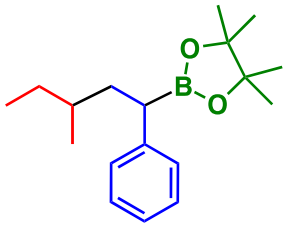

**(1-Chloro-3-methylpentyl)benzene:** Obtained from styrene and $CCl_4$ as the styrene monomer and electrophile in 84% yield (GC yield) and mixture of two diastereomers. Yields were determined by GC analysis using an internal standard ($C_{12}H_{26}$). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 44% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$, diastereomer ratio = 50:50) δ 7.40-7.25 (m, 5H), 4.97-4.93 (m, 1H), 2.16 (ddd, *J* = 13.6, 10.0, 4.4 Hz, 0.50H), 2.06 (ddd, *J* = 13.6, 7.6, 6.0 Hz, 0.50H), 1.96 (ddd, *J* = 14.0, 7.2, 7.2 Hz, 0.50H), 1.74-1.58 (m, 1H), 1.44-1.32 (m, 1.50H), 1.28-1.13 (m, 1H), 0.93-0.80 (m, 6H); $^{13}$C NMR (100MHz, $CDCl_3$, diastereomer ratio = 50:50) δ 142.6-141.9 (1C), 128.7 (2C), 127.3-127.2 (1C), 127.1-127.0 (2C), 62.3-62.0 (1C), 47.0-46.9 (1C), 32.0-31.9 (1C), 29.6-28.9 (1C), 19.0-18.5 (1C), 11.2-11.0 (1C). HRMS (EI) *m/z* Calcd for $C_{12}H_{17}Cl[M]^+$ 196.1013; Found: 196.1018.



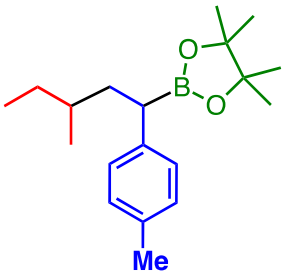

**Trimethyl(3-methyl-1-phenylpentyl)silane:** Obtained from styrene and TMSCl as the styrene monomer and electrophile in 86% yield (GC yield) and mixture of two diastereomers. Yields were determined by GC analysis using an internal standard ($C_{12}H_{26}$). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$, diastereomer ratio = 54:46) to give the product in 31% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$, diastereomer ratio = 54:46) δ 7.26-7.00 (m, 5H), 2.18-2.10 (m, 1H), 1.97-1.91 (m, 0.54H), 1.74 (ddd, *J* = 14.0, 12.4, 4.0 Hz, 0.46H), 1.56-0.98 (m, 4H), 0.83-0.76 (m, 6H), -0.08 (s, 9H); $^{13}$C NMR (100MHz, $CDCl_3$, diastereomer ratio = 54 : 46) δ 144.3-143.8 (1C), 128.0 (2C), 127.9 (2C), 124.2 (1C), 36.3-35.8 (1C), 34.3-34.1 (1C), 32.4-32.3 (1C), 30.8-27.2 (1C), 20.2-18.1 (1C), 11.6-10.6 (1C), -2.9 (3C). HRMS (EI) *m/z* Calcd for $C_{15}H_{26}Si$ $[M]^+$ 234.1802; Found: 234.1804.



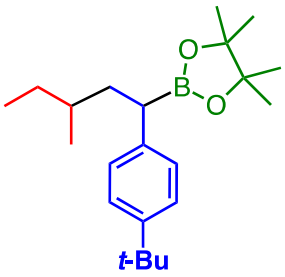

**Tributyl(3-methyl-1-phenylpentyl)stannane:** Obtained from styrene and $Bu_3SnCl$ as the styrene monomer and electrophile in 79% yield (GC yield) and mixture of two diastereomers. Yields were determined by GC analysis using an internal standard ($C_{12}H_{26}$). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$, diastereomer ratio = 49:51) to give the product in 17% isolated yield. 7.18 (dd, *J* = 8.0, 8.0 Hz, 2H),7.03-6.95 (m, 3H), 2.78-2.69 (m, 1H), 2.17 (ddd, *J* = 14.8, 12.0, 3.6 Hz, 0.49H), 1.92 (ddd, *J* = 13.6, 10.0, 6.0 Hz, 0.51H), 1.78 (ddd, *J* = 13.6, 13.6, 6.4 Hz, 0.51H), 1.42-1.07 (m, 15.49H), 0.92-0.78 (m, 15H), 0.78-0.66 (m, 6H); $^{13}$C NMR (100MHz, $CDCl_3$, diastereomer ratio = 49:51) δ 147.4-146.8 (1C), 128.2 (2C), 126.4 (t, 11.5 Hz, 2C), 123.2 (1C), 39.3-38.7 (1C), 33.4-33.0 (1C), 31.9-31.2 (1C), 30.3-28.2 (1C), 29.2 (t, 9.6 Hz, 3C), 27.6 (t, 26.8 Hz, 3C), 19.9-18.3 (1C), 13.8 (3C), 11.5-11.0 (1C), 10.4-7.4 (m, 3C). HRMS (EI) *m/z* Calcd for $C_{20}H_{35}Sn[M\text{-}Bu]^+$ 395.1761; Found: 395.1760.



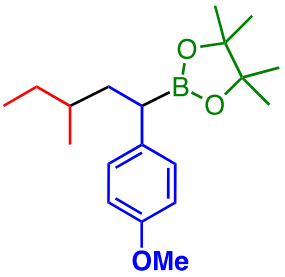

**4,4,5,5-Tetramethyl-2-(3-methyl-1-phenylpentyl)-1,3,2-dioxaborolane:** Obtained from styrene and *i*PrOBpin (2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane) as the styrene monomer and electrophile in 85% yield (GC yield) and mixture of two diastereomers. Yields were determined by GC analysis using an internal standard ($C_{12}H_{26}$). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 67% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$, diastereomer ratio = 48:52) δ 7.25-7.10 (m, 5H), 2.46-2.40 (m, 1H), 1.86 (ddd, *J* = 13.2, 8.8, 5.6 Hz, 0.48H), 1.74 (ddd, *J* = 13.6, 7.6, 6.4 Hz, 0.52H), 1.57 (ddd, *J* = 13.6, 8.8, 7.2 Hz, 0.52H), 1.49-1.06 (m, 15.48H), 0.87-0.79 (m, 6H); $^{13}$C NMR (100MHz, $CDCl_3$, diastereomer ratio = 48:52) δ 143.8-143.5 (1C), 128.5-128.3 (4C), 125.1 (1C), 83.3 (2C), 39.8-39.1 (1C), 33.8-33.1 (1C), 30.0 (1C, broad), 29.8-29.3 (1C), 24.7 (4C), 19.5-18.9 (1C), 11.4 (1C). HRMS (APCI) *m/z* Calcd for $C_{18}H_{29}BO_2$ $[M]^+$ 287.2291; Found: 287.2298.




**4,4,5,5-Tetramethyl-2-(3-methyl-1-(p-tolyl)pentyl)-1,3,2-dioxaborolane:** Obtained from 1-methyl-4-vinylbenzene and *i*PrOBpin as the styrene monomer and electrophile in 91% yield (GC yield) and mixture of two diastereomers. Yields were determined by GC analysis using an internal standard ($C_{12}H_{26}$). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 70% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$, diastereomer ratio = 47:53) δ 7.12-7.02 (m, 4H), 2.41-2.38 (m, 1H), 2.29 (s, 3H), 1.84 (ddd, *J* = 13.2, 9.2, 6.4 Hz, 0.47H), 1.71 (ddd, *J* = 13.6, 9.2, 5.2 Hz, 0.53H), 1.55 (ddd, *J* = 15.2, 8.4, 7.6 Hz, 0.53H), 1.46-1.08 (m, 15.47H), 0.86-0.79 (m, 6H); $^{13}$C NMR (100MHz, $CDCl_3$, diastereomer ratio = 47:53) δ 140.7-140.3 (1C), 134.4-134.3 (1C), 129.1 (2C), 128.4-128.3 (2C), 83.2 (2C), 40.1-39.3 (1C), 33.8-33.1 (1C), 29.8-29.4 (1C), 29.4 (1C, broad), 24.8-24.7 (4C), 21.1 (1C), 19.6-18.9 (1C), 11.4 (1C). HRMS (ESI) *m/z* Calcd for $C_{19}H_{31}O_2BNa$ $[M+Na]^+$ 324.2346; Found: 324.2341.

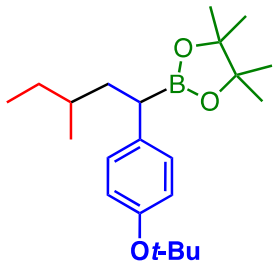



**2-(1-(4-(tert-Butyl)phenyl)-3-methylpentyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane:** Obtained from 1-(tert-butyl)-4-vinylbenzene and *i*PrOBpin as the styrene monomer and electrophile in 86% yield (GC yield) and two mixture of diastereomers. Yields were determined by GC analysis using an internal standard ($C_{12}H_{26}$). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 70% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$, diastereomer ratio = 46:54) δ 7.24 (dd, *J* = 8.4, 2.4 Hz, 2H), 7.12 (t, *J* = 8.0 Hz, 2H), 2.43-2.36 (m, 1H), 1.87 (ddd, *J* = 12.8, 9.6, 5.6 Hz, 0.46H), 1.68 (ddd, *J* = 14.4, 8.4, 6.0 Hz, 0.54H), 1.62-1.57 (m, 0.54H), 1.45-1.29 (m, 11.46H), 1.26-1.06 (m, 13H), 0.89-0.79 (m, 6H); $^{13}$C NMR (100MHz, $CDCl_3$, diastereomer ratio = 46:54) δ 147.6 (1C), 140.7-140.3 (1C), 128.0 (2C), 125.2 (2C), 83.2 (2C), 40.2-39.6 (1C), 34.3 (1C), 34.0-33.3 (1C), 31.6 (3C), 29.6 (1C), 29.5 (1C, broad), 24.8-24.7 (4C), 19.5-19.1 (1C), 11.4 (1C). HRMS (ESI) *m/z* Calcd for $C_{22}H_{37}O_2BNa$ $[M+Na]^+$ 366.2815; Found: 366.2812.

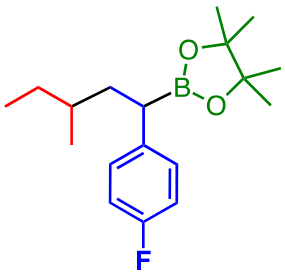



**2-(1-(4-Methoxyphenyl)-3-methylpentyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane:** Obtained from 1-methoxy-4-vinylbenzene and *i*PrOBpin as the styrene monomer and electrophile in 83% yield (GC yield) and mixture of two diastereomers. Yields were determined by GC analysis using an internal standard ($C_{12}H_{26}$). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 62% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$, diastereomer ratio = 44:56) δ 7.13 (t, *J* = 8.8 Hz, 2H), 6.80 (d, *J* = 8.8 Hz, 2H) 3.78 (s, 3H), 2.40-2.34 (m, 1H), 1.82 (ddd, *J* = 13.2, 9.2, 6.4 Hz, 0.44H), 1.69 (ddd, *J* = 13.6, 9.2, 5.6 Hz, 0.56H), 1.59-1.06 (m, 16H), 0.87-0.79 (m, 6H); $^{13}$C NMR (100MHz, $CDCl_3$, diastereomer ratio = 44:56) δ 157.3 (1C), 135.7-135.4 (1C), 129.2 (2C), 113.7 (2C), 83.2 (2C), 55.1 (1C), 40.1-39.4 (1C),

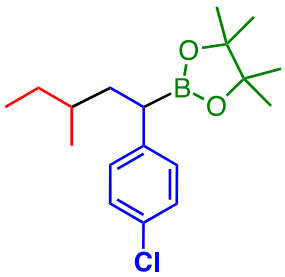
33.7-33.0 (1C), 29.8-29.3 (1C), 29.2 (1C, broad), 24.7 (4C), 19.6-18.9 (1C), 11.4 (1C). HRMS (ESI) *m/z* Calcd for $C_{19}H_{31}O_3BNa$ $[M+Na]^+$ 340.2295; Found: 340.2289.




**2-(1-(4-(tert-Butoxy)phenyl)-3-methylpentyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane:** Obtained from 1-(tert-butoxy)-4-vinylbenzene and *i*PrOBpin as the styrene monomer and electrophile in 84% yield (GC yield) and mixture of two diastereomers. Yields were determined by GC analysis using an internal standard ($C_{12}H_{26}$). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 63% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$, diastereomer ratio = 46:54) δ 7.09 (dd, *J* = 8.0, 6.8 Hz, 2H), 6.86 (d, *J* = 8.4 Hz, 2H), 2.42-2.35 (m, 1H), 1.87 (ddd, *J* = 13.2, 9.6, 5.2 Hz, 0.46H), 1.69 (ddd, *J* = 13.6, 8.0, 5.2 Hz, 0.54H), 1.61-1.08 (m, 25H), 0.88-0.79 (m, 6H); $^{13}$C NMR (100MHz, $CDCl_3$, diastereomer ratio = 46:54) δ 152.7 (1C), 138.8-138.3 (1C), 128.5 (2C), 124.1 (2C), 83.1 (2C), 77.9 (1C), 39.5-39.0 (1C), 34.0-33.3 (1C), 29.6-29.5 (1C), 29.1 (1C, broad), 28.9 (4C), 24.6-24.5 (3C), 19.5-19.1 (1C), 11.4 (1C). HRMS (ESI) *m/z* Calcd for $C_{22}H_{37}O_3BNa$ $[M+Na]^+$ 382.2764; Found: 382.2758.

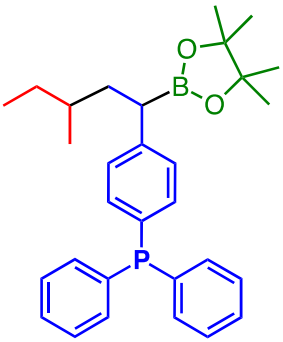



**2-(1-(4-Fluorophenyl)-3-methylpentyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane:** Obtained from 1-fluoro-4-vinylbenzene and *i*PrOBpin as the styrene monomer and electrophile in 70% yield (GC yield) and mixture of two diastereomers. Yields were determined by GC analysis using an internal standard ($C_{12}H_{26}$). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 45% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$, diastereomer ratio = 46:54) δ 7.18-7.12 (m, 2H), 6.93 (tt, *J* = 8.8, 2.0 Hz, 2H), 2.43-2.37 (m, 1H), 1.83 (ddd, *J* = 13.2, 9.2, 6.0 Hz, 0.46H), 1.69 (ddd, *J* = 13.6, 8.8, 4.8 Hz, 0.54H), 1.55 (ddd, *J* = 13.6, 8.0, 6.8 Hz, 0.54H), 1.45-1.06 (m, 15.46H), 0.87-0.79 (m, 6H); $^{13}$C NMR (100MHz, $CDCl_3$, diastereomer ratio = 46:54) δ 160.9 (d, *J* = 241 Hz, 1C), 139.4-139.0 (1C), 129.7-129.5 (2C), 115.0 (d, *J* = 20 Hz, 2C), 83.3 (2C), 39.9-39.2 (1C), 33.7-33.0 (1C), 29.8-29.2 (1C), 29.0 (1C, broad), 24.7-24.6 (4C), 19.5-18.8 (1C), 11.4-11.3 (1C). HRMS (EI) *m/z* Calcd for $C_{18}H_{28}O_2BF$ $[M]^+$ 305.2197; Found: 305.2191.

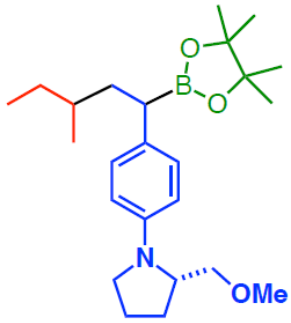



**2-(1-(4-Chlorophenyl)-3-methylpentyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane:** Obtained from 1-chloro-4-vinylbenzene and *i*PrOBpin as the styrene monomer and electrophile in 42% yield (GC yield) and mixture of two diastereomers. Yields were determined by GC analysis using an internal standard ($C_{12}H_{26}$). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 26% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$, diastereomer ratio = 49:51) δ 7.21-7.11 (m, 4H), 2.43-2.37 (m, 1H), 1.83 (ddd, *J* = 13.2, 8.4, 5.6 Hz, 0.49H), 1.70 (ddd, *J* = 13.2, 9.2, 4.8 Hz, 0.51H), 1.55 (ddd, *J* = 14.0, 8.4, 6.8 Hz, 0.51H),

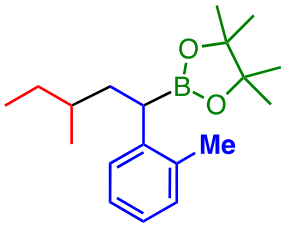
1.50-1.24 (m, 2.49H), 1.21-1.06 (m, 13H), 0.87-0.75 (m, 6H); $^{13}$C NMR (100MHz, $CDCl_3$, diastereomer ratio = 49:51) δ 142.4-142.0 (1C), 130.8 (1C), 129.8-129.7 (2C), 128.4 (2C), 83.4 (2C), 39.6-38.9 (1C), 33.6-33.0 (1C), 29.8-29.1 (1C), 29.1 (1C, broad), 24.7-24.6 (4C), 19.5-18.7 (1C), 11.3 (1C). HRMS (EI) *m/z* Calcd for $C_{18}H_{28}O_2BCl$ $[M]^+$ 321.1902; Found: 321.1899.



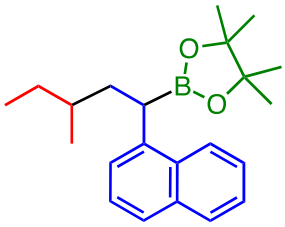

**(4-(3-Methyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentyl)phenyl)diphenylphosphane:** Obtained from diphenyl(4-vinylphenyl)phosphane and *i*PrOBpin as the styrene monomer and electrophile in 85% yield (GC yield) and mixture of two diastereomers. Yields were determined by GC analysis using an internal standard ($C_{12}H_{26}$). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 30% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$, diastereomer ratio = 45:55) δ 7.33-7.17 (m, 14H), 2.47-2.41 (m, 1H), 1.87 (ddd, *J* = 14.0, 9.6, 6.0 Hz, 0.45H), 1.72 (ddd, *J* = 13.6, 8.8, 5.6 Hz, 0.55H), 1.63-1.55 (m, 0.55H), 1.48-1.07 (m, 15.45H), 0.87-0.79 (m, 6H); $^{13}$C NMR (100MHz, $CDCl_3$, diastereomer ratio = 45:55) δ 144.8-144.5 (1C), 137.7-128.3 (14C), 83.2 (2C), 39.3-38.7 (1C), 33.8-33.1 (1C), 29.8 (1C, broad), 29.5-29.2 (1C), 24.5 (4C), 19.4-18.8 (1C), 11.2 (1C); $^{31}$P NMR (162 MHz, $CDCl_3$) δ -5.7 (s, 1P). HRMS (EI) *m/z* Calcd for $C_{30}H_{39}O_2BP$ $[M]^+$ 472.2812; Found: 472.2801.



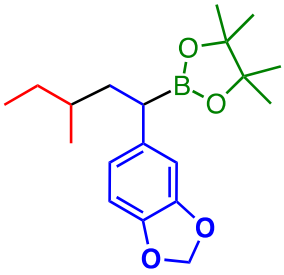

**(2S)-2-(Methoxymethyl)-1-(4-(3-methyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentyl)benzyl)pyrrolidine:** Obtained from (S)-2-(methoxymethyl)-1-(4-vinylbenzyl)pyrrolidine and *i*PrOBpin as the styrene monomer and electrophile in 66% yield (GC yield) and mixture of diastereomers. Yields were determined by GC analysis using an internal standard ($C_{12}H_{26}$). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 24% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$, diastereomer mixtures) δ 7.22-7.13 (m, 4H), 4.02 (d, *J* = 12.8, 1H) 3.47-3.43 (m, 2H), 3.36-3.28 (m, 4H), 2.99 (t, *J* = 8.0, 1H), 2.76 (qu, *J* = 13.6, 1H), 2.44-2.38 (m, 1H), 2.30-2.24 (m, 1H), 1.97-1.38 (m, 6H), 1.38-1.06 (m, 15H), 0.87-0.79 (m, 6H); $^{13}$C NMR (100MHz, $CDCl_3$, diastereomer mixture) δ 142.6-142.3 (1C), 135.2 (1C), 129.3 (2C), 128.3-128.2 (2C), 83.2 (2C), 76.0 (1C), 63.2 (1C), 59.4 (1C), 59.1 (1C), 54.7-54.6 (1C), 39.8-39.0 (1C), 33.7-33.1 (1C), 29.7-29.2 (1C), 29.0 (1C, broad), 28.5 (1C), 24.6 (4C), 22.8 (1C), 19.5-18.8 (1C), 11.3 (1C). HRMS (EI) *m/z* Calcd for $C_{25}H_{43}O_3NB$ $[M]^+$ 415.3367; Found: 415.3365.




**4,4,5,5-Tetramethyl-2-(3-methyl-1-(o-tolyl)pentyl)-1,3,2-dioxaborolane:** Obtained from 1-methyl-2-vinylbenzene and *i*PrOBpin as the styrene monomer and electrophile in 77% yield (GC yield) and mixture of two diastereomers. Yields were determined by GC analysis using an internal standard ($C_{12}H_{26}$). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 16% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$, diastereomer ratio = 51:49) δ 7.26-6.99 (m, 4H), 2.63-2.60 (m, 1H), 2.33 (s, 3H), 1.90 (ddd, *J* = 12.8, 10.0, 4.8 Hz, 0.51H), 1.73 (ddd, *J* = 14.0, 8.4, 5.6 Hz, 0.49H), 1.62 (dt, *J* = 13.2, 8.0 Hz, 0.49H), 1.42-1.16 (m, 15.51H), 0.90-0.81 (m, 6H); $^{13}$C NMR (100MHz, $CDCl_3$, diastereomer ratio = 51:49) δ 142.3-141.9 (1C), 136.0-135.9 (1C), 130.2-130.1 (1C), 127.8 (1C), 126.0-125.9 (1C), 124.9-124.8 (1C), 83.2 (2C), 39.5-38.7 (1C), 34.2-33.6 (1C), 29.8-29.7 (1C), 29.7 (1C, broad), 24.8-24.6 (4C), 20.3-20.2 (1C), 19.5-19.3 (1C), 11.4 (1C). HRMS (ESI) *m/z* Calcd for $C_{19}H_{31}O_2BNa$ $[M+Na]^+$ 324.2346; Found: 324.2343.



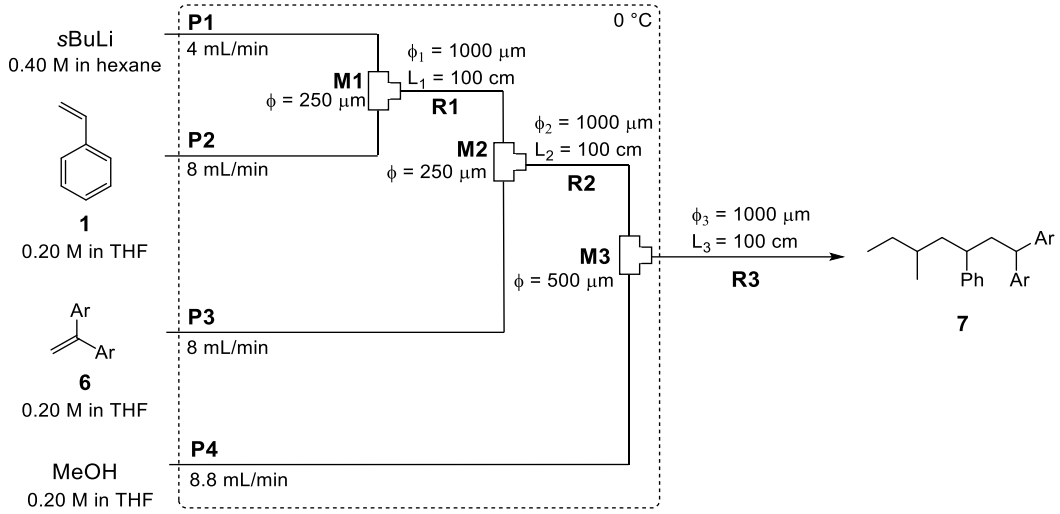

**4,4,5,5-Tetramethyl-2-(3-methyl-1-(naphthalen-2-yl)pentyl)-1,3,2-dioxaborolane:** Obtained from 2-vinylnaphthalene and *i*PrOBpin as the styrene monomer and electrophile in 67% yield (GC yield) and mixture of two diastereomers. Yields were determined by GC analysis using an internal standard ($C_{12}H_{26}$). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 58% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$, diastereomer ratio = 50:50) δ 8.21-8.19 (m, 1H), 8.79 (d, *J* = 8.0 Hz, 1H), 7.63 (d, *J* = 8.4 Hz, 1H), 7.48-7.36 (m, 4H), 3.21-3.17 (m, 1H), 2.12-2.06 (m, 0.50H), 1.95-1.89 (m, 0.50H), 1.86-1.77 (m, 0.50H), 1.63-1.57 (m, 0.50H), 1.49-1.32 (m, 2H), 1.24-1.12 (m, 13H), 0.96-0.80 (m, 6H); $^{13}$C NMR (100MHz, $CDCl_3$, diastereomer ratio = 50:50) δ 140.6-140.3 (1C), 134.2 (1C), 132.4 (1C), 128.9 (1C), 125.9-125.2 (5C), 124.4-124.3 (1C), 83.5 (2C), 39.6-39.1 (1C), 34.3-33.7 (1C), 29.9-29.7 (1C), 25.6 (1C, broad), 24.9-24.7 (4C), 19.6-19.4 (1C), 11.6-11.5 (1C). HRMS (ESI) *m/z* Calcd for $C_{22}H_{31}O_2BNa$ $[M+Na]^+$ 360.2346; Found: 360.2339.



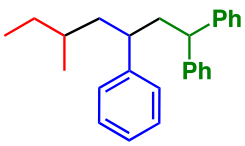

**2-(1-(Benzo[d][1,3]dioxol-5-yl)-3-ethylpentyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane:** Obtained from 5-vinylbenzo[d][1,3]dioxole and *i*PrOBpin as the styrene monomer and electrophile in 83% yield (GC yield) and mixture of two diastereomers. Yields were determined by GC analysis using an internal standard ($C_{12}H_{26}$). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 55% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$, diastereomer ratio = 46:54) δ 6.75-6.62 (m, 3H), 5.88 (s, 2H), 2.37-2.32 (m, 1H), 1.80 (ddd, *J* = 13.2, 9.2, 6.0 Hz, 0.46H), 1.67 (ddd, *J* = 14.0, 8.8, 4.8 Hz, 0.54H), 1.52 (dt, *J* = 15.2, 7.2 Hz, 0.54H), 1.44-1.06 (m, 15.46H), 0.87-0.79 (m, 6H); $^{13}$C NMR (100MHz, $CDCl_3$, diastereomer ratio = 46:54) δ 147.5 (1C), 145.1 (1C), 137.7-137.3 (1C),

121.2-121.0 (1C), 108.9 (1C), 108.1 (1C), 100.6 (1C), 83.3 (2C), 40.1-39.4 (1C), 33.6-33.0 (1C), 29.8-29.2 (1C), 29.1 (1C, broad), 24.6 (4C), 19.5-18.8 (1C), 11.3 (1C). HRMS (ESI) *m/z* Calcd for $C_{19}H_{29}O_4BNa$ $[M+Na]^+$ 354.2087; Found: 354.2921.

### 2-5-3. Synthesis of an Adduct of Styrene and Diphenylethylene.

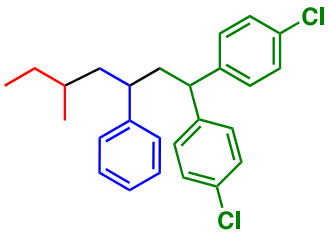



A flow microreactor system consisting of three T-shaped micromixers (**M1**, **M2**, and **M3**), three microtube reactors (**R1**, **R2**, and **R3**), and four pre-cooling units (**P1** (L = 50 cm), **P2** (100 cm), **P3** (100 cm), and **P4** (100 cm)) was used in a cooling bath at 0 °C. A solution of *s*-BuLi (0.40 M in hexane, flow rate: 4.0 mL/min) and a solution of styrene (**1**, 0.20 M in THF, flow rate: 8.0 mL/min) were introduced to **M1** ($\phi$ = 250 μm) using syringe pumps, and the mixture was passed through **R1** (100 cm, residence time $t^{R1}$ = 3.9 s). The resulting solution was introduced to **M2** ($\phi$ = 250 μm), where a solution of diphenyl ethylene monomer (0.20 M in THF) was also introduced (flow rate: 8.0 mL/min). The resulting solution was passed through **R2** ($\phi$ = 1000 μm, L = 100 cm, residence time = 2.4 s). The resulting solution was introduced to **M3** ($\phi$ = 500 μm), where a solution of methanol (0.20 M in THF) was also introduced (flow rate: 8.8 mL/min). The resulting solution was passed through **R3** ($\phi$ = 1000 μm, L = 100 cm, residence time = 1.6 s). After a steady state was reached, the product solution was collected for 30 seconds. To the aliquot, sat. $NH_4Cl$ aq. was added, and then the organic phase was analyzed by GC and GPC.

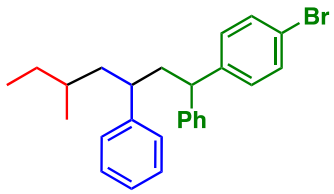



**(5-methylheptane-1,1,3-triyl)tribenzene:** Obtained from diphenyl ethylene as the diphenyl ethylene monomer in 85% yield (GC yield). Yields were determined by GC analysis using an internal standard ($C_{12}H_{26}$). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$, diastereomer mixtures) to give the product in 55% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.29-7.03 (m, 15H), 3.72-3.66 (m, 1H), 2.55-2.46 (m, 1H), 2.44-

2.35 (m, 1H), 2.26-2.15 (m, 1H), 1.69-1.56 (m, 1H), 1.43-1.33 (m, 1H), 1.30-0.94 (m, 3H), 0.76-0.68 (m, 6H); $^{13}$C NMR (100MHz, $CDCl_3$, diastereomer mixtures) δ 146.1-145.6 (2C), 144.3-144.2 (1C), 128.6-127.8 (12C), 126.4 (1C), 126.2-126.1 (2C), 48.8 (1C), 44.9-44.3 (1C), 43.9-42.8 (1C), 41.0 (1C), 31.8 (1C), 30.3-29.0 (1C), 19.7-19.0 (1C), 11.4-11.1 (1C). HRMS (EI) *m/z* Calcd for $C_{26}H_{30}$ $[M]^+$ 342.2342; Found: 342.2334.

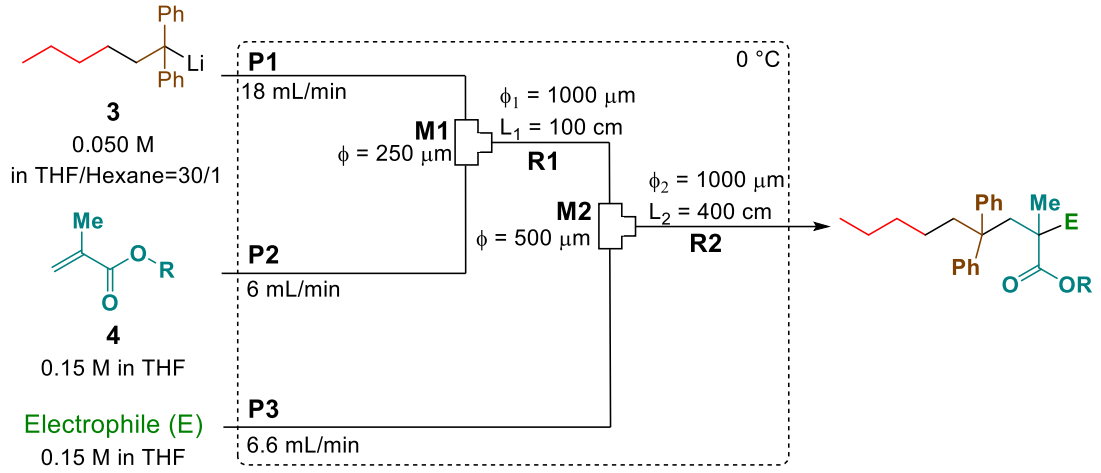



**4,4'-(5-methyl-3-phenylheptane-1,1-diyl)bis(chlorobenzene):** Obtained from 4,4'-(ethene-1,1-diyl) bis(chlorobenzene) as the diphenyl ethylene monomer in 80% yield (GC yield). Yields were determined by GC analysis using an internal standard ($C_{12}H_{26}$). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 54% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$, diastereomer mixtures) δ 7.30-6.97 (m, 13H), 3.63-3.58 (m, 1H), 2.50-2.42 (m, 1H), 2.38-2.27 (m, 1H), 2.19-2.09 (m, 1H), 1.69-1.54 (m, 1H), 1.43-1.30 (m, 1H), 1.28-0.94 (m, 3H), 0.77-0.69 (m, 6H); $^{13}$C NMR (100MHz, $CDCl_3$, diastereomer mixtures) δ 145.5-145.0 (1C), 143.9-143.8 (1C), 142.3-142.2 (1C), 132.3 (1C), 132.0 (1C), 129.7-127.9 (12C), 126.4 (1C), 47.5 (1C), 44.9-44.3 (1C), 43.6-42.5 (1C), 41.0 (1C), 31.8 (1C), 30.3-28.9 (1C), 19.7-18.9 (1C), 11.3-11.1 (1C). HRMS (EI) *m/z* Calcd for $C_{26}H_{28}Cl_2$ $[M]^+$ 410.1563; Found: 410.1568

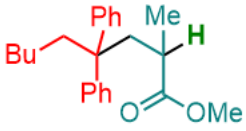



**(1-(4-bromophenyl)-5-methylheptane-1,3-diyl)dibenzene:** Obtained from 1-bromo-4-(1-phenylethyl) benzene as the diphenyl ethylene monomer in 85% yield (GC yield). Yields were determined by GC analysis using an internal standard ($C_{12}H_{26}$). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 56% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$, diastereomer mixtures) δ 7.39-6.95(m, 14H), 3.65-3.60 (m, 1H), 2.50-2.30 (m, 2H), 2.24-2.09 (m, 1H), 1.68-1.55 (m, 1H), 1.43-1.32 (m, 1H), 1.29-0.96 (m, 3H), 0.76-0.68 (m, 6H); $^{13}$C NMR (100MHz, $CDCl_3$, diastereomer mixtures) δ 145.9-144.9 (2C), 143.7-143.2 (1C), 131.8-126.4 (14C), 120.2-119.9 (1C), 48.3 (1C), 45.0-44.3 (1C), 43.8-42.6 (1C), 41.0 (1C), 31.8 (1C), 30.3-29.0 (1C), 19.8-19.0 (1C), 11.4-11.1 (1C). HRMS (EI) *m/z* Calcd for $C_{26}H_{29}Br$ $[M]^+$ 420.1447; Found: 420.1456.

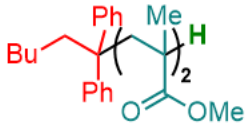
## 2-5-4. Synthesis Methacrylate Monoaddition product in a Flow Microreactor




A flow microreactor system consisting of two T-shaped micromixers (**M1** and **M2**), two microtube reactors (**R1** and **R2**), and three pre-cooling units (**P1** (L = 100 cm), **P2** (100 cm) and **P3** (100 cm)) was used in a cooling bath at 0 °C. A solution of diphenylhexyl lithium (**3**, 0.050 M in THF/hexane=30/1, flow rate: 18 mL/min) and a solution of methacrylate monomer (**4**, 0.15 M in THF, flow rate: 6.0 mL/min) were introduced to **M1** ($\phi$ = 250 μm) using syringe pumps, and the mixture was passed through **R1** ($\phi$ = 1000 μm, 100 cm, residence time $t^{R1}$ = 2.0 s). The resulting solution was introduced to **M2** ($\phi$ = 500 μm), where a solution of electrophile (0.15 M in THF) was also introduced (flow rate: 6.6 mL/min). The resulting solution was passed through **R2** ($\phi$ = 1000 μm, L = 400 cm, residence time = 6.2 s). After a steady state was reached, the product solution was collected for 10 seconds. To the aliquot, sat. $NH_4Cl$ aq. was added, and then the organic phase was analyzed by GC and NMR.




**Methyl 2-methyl-4,4-diphenylnonanoate:** Obtained from methyl methacrylate and $CH_3OH$ as the methacrylate monomer and electrophile in 90% yield (GC yield). Yields were determined by GC analysis using an internal standard ($C_{12}H_{26}$). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 69% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.25-7.10 (m, 10H), 3.36 (s, 3H), 2.80 (dd, *J* = 14.4, 8.4 Hz, 1H), 2.29 (dqd, *J* = 7.2, 6.8, 2.8 Hz, 1H), 2.13-2.06 (m, 2H), 2.00 (dt, *J* = 13.2, 4.4 Hz, 1H), 1.24-1.14 (m, 4H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.96-0.82 (m, 2H), 0.79 (t, *J* = 7.2 Hz, 3H); $^{13}$C NMR (100MHz, $CDCl_3$) δ 177.5, 148.5, 147.9, 128.3 (2C), 128.1 (2C), 127.9 (2C), 127.8 (2C), 125.8 (2C), 51.5, 49.5, 41.6, 38.0, 35.9, 35.6, 23.8, 22.6, 20.5, 14.1. HRMS (ESI) *m/z* Calcd for $C_{23}H_{30}O_2Na$ $[M+Na]^+$ 361.2138; Found: 361.2127.




**Dimethyl 2-(2,2-diphenylheptyl)-2,4-dimethylpentanedioate:** Obtained from methyl methacrylate and $CH_3OH$ as the methacrylate monomer and electrophile in 17% yield (GC yield) and mixture of two diastereomers. Yields were determined by GC analysis using an internal standard ($C_{12}H_{26}$). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 2% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$, diastereomer ratio = 84:16) δ 7.25-7.11 (m, 10H), 3.63-3.61 (m, 3H), 3.38-3.35 (m, 3H), 2.86-2.79 (m, 1H), 2.47-2.15 (m, 4H), 1.99-1.89 (m, 1H), 1.33-1.04 (m, 10H), 0.88-0.85 (m, 3H), 0.79-0.77 (m, 3H); $^{13}$C NMR (100MHz, $CDCl_3$, diastereomer ratio = 84:16) δ 177.3, 176.7, 149.3, 148.4, 128.5 (2C), 128.4 (2C), 127.7 (2C), 127.6 (2C), 125.7 (2C), 51.7, 51,5, 49.4, 47.0, 46.9, 45.3, 38.2, 33.5, 32.5, 24.2, 22.6, 20.9, 20.3, 14.2. HRMS (ESI) *m/z* Calcd for $C_{24}H_{32}O_2Na$ $[M+Na]^+$ 375.2295; Found: 375.2286.

Similarly, in the case of the monoaddition reaction to methacrylic ester, the GPC chart showed a high degree of polymerization control in the flow (Figure S3). Next, an oligomer synthesis study was conducted to increase the amount of MMA equivalent added by changing the concentration of the MMA solution (Table S2). As in the case of styrene, the peak moved toward the high molecular weight side as the MMA equivalent was increased (Figure S4), and oligomers with a controlled molecular weight distribution could be synthesized. In all cases, a slight peak appeared at the same position as the monoadduct peak, which is thought to be a byproduct of the nucleophilic attack of DPHLi on the ester moiety of the methacrylate (Scheme S1).

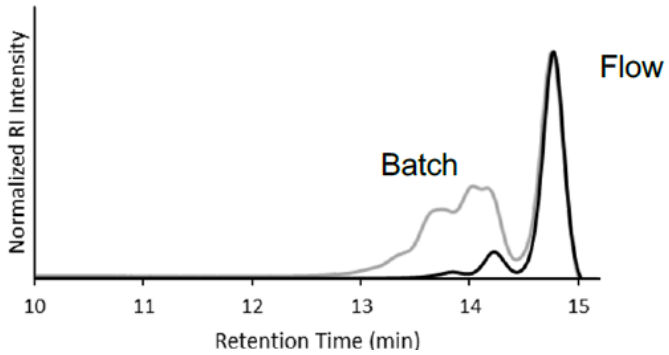
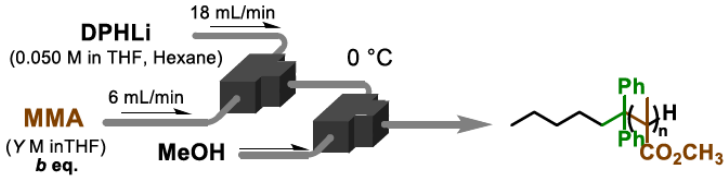



**Figure 5.** GPC chart for MMA monoadduct synthesis study

**Table 7**. Oligomer synthesis by changing MMA equivalents




| ***b* (eq.)** | *Y* (M) | $M_n$ | **PDI** | Conv. (%) |
|---|---|---|---|---|
| **1** | 0.15 | 330 | **1.04** | 100 |
| **2** | 0.30 | 410 | **1.06** | 100 |
| **3** | 0.45 | 570 | **1.05** | 100 |
| **4** | 0.60 | 640 | **1.04** | 100 |
| **5** | 0.75 | 680 | **1.05** | 100 |
| **6** | 0.90 | 840 | **1.07** | 100 |
| **7** | 1.05 | 940 | **1.10** | 100 |
| **8** | 1.20 | 950 | **1.11** | 100 |
| **9** | 1.35 | 1000 | **1.13** | 100 |
| **10** | 1.50 | 1100 | **1.13** | 100 |
| **15** | 2.25 | 1500 | **1.21** | 100 |

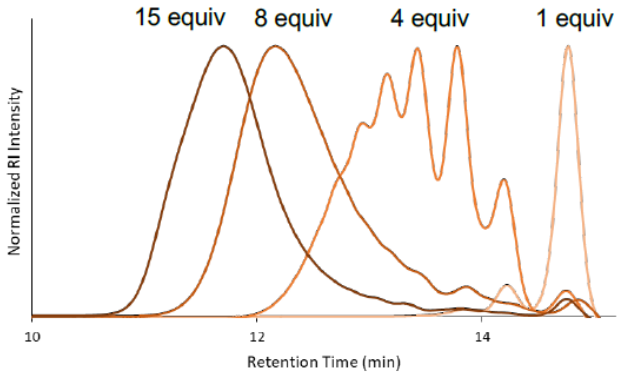
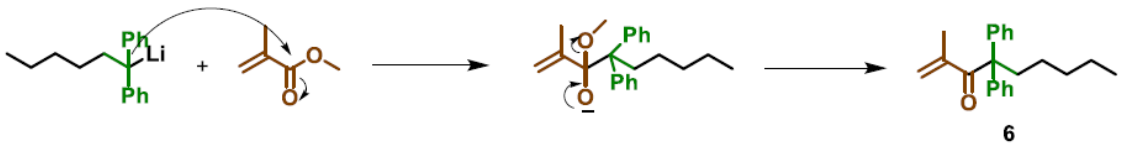
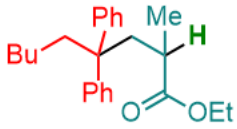



**Figure 6.** GPC chart for MMA oligomer synthesis

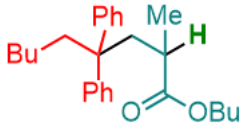
**Scheme 6.**



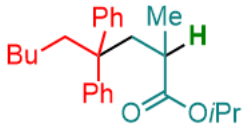

**6**



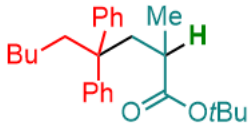

**Ethyl 2-methyl-4,4-diphenylnonanoate:** Obtained from ethyl methacrylate and $CH_3OH$ as the methacrylate monomer and electrophile in 82% yield (GC yield). Yields were determined by GC analysis using an internal standard ($C_{12}H_{26}$). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 49% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.25-7.10 (m, 10H), 3.87-3.74 (m, 2H), 2.81 (dd, *J* = 14.0, 8.4 Hz, 1H), 2.26 (qud, *J* = 6.8, 2.8 Hz, 1H), 2.12-1.97 (m, 3H), 1.26-1.16 (m, 4H), 1.13 (t, *J* = 7.2 Hz, 3H), 1.04-1.00 (m, 1H), 0.98 (d, *J* = 7.2 Hz , 3H), 0.94-0.82 (m, 1H), 0.79 (t, *J* = 7.2 Hz, 3H); $^{13}$C NMR (100MHz, $CDCl_3$) δ 177.2, 148.5, 148.0, 128.3 (2C), 128.1 (2C), 127.9 (2C), 127.7 (2C), 125.8 (2C), 60.2, 49.5, 41.5, 38.0, 35.9, 32.6, 23.8, 22.6, 20.5, 14.1 (2C). HRMS (ESI) *m/z* Calcd for $C_{24}H_{32}O_2Na$ $[M+Na]^+$ 375.2295; Found: 375.2288.



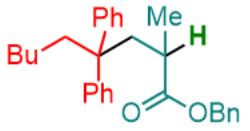

**Butyl 2-methyl-4,4-diphenylnonanoate :** Obtained from *n*-butyl methacrylate and $CH_3OH$ as the methacrylate monomer and electrophile in 80% yield (GC yield). Yields were determined by GC analysis using an internal standard ($C_{12}H_{26}$). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 71% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.24-7.10 (m, 10H), 3.83-3.72 (m, 2H), 2.83 (dd, *J* = 13.6, 7.6 Hz, 1H), 2.29-2.24 (m, 1H), 2.12-1.97 (m, 3H), 1.50 (qu, *J* = 7.6 Hz, 2H), 1.32 (sext, *J* = 7.6 Hz, 2H), 1.25-1.12 (m, 4H), 1.06-0.99 (m, 1H), 0.97 (d, *J* = 6.8 Hz , 3H), 0.91 (t, *J* = 7.2 Hz, 3H), 0.89-0.84 (m, 1H), 0.79 (t, *J* = 6.8 Hz, 3H); $^{13}$C NMR (100MHz, $CDCl_3$) δ 177.2, 148.5, 148.1, 128.3 (2C), 128.2 (2C), 127.9 (2C), 127.8 (2C), 125.8 (2C), 64.2, 49.6, 41.5, 38.0, 36.0, 32.6, 30.7, 23.8, 22.6, 20.5, 19.3, 14.1, 13.9. HRMS (ESI) *m/z* Calcd for $C_{26}H_{36}O_2Na$ $[M+Na]^+$ 403.2608; Found: 403.2603.



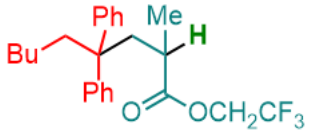

**Isopropyl 2-methyl-4,4-diphenylnonanoate :** Obtained from *iso*-propyl methacrylate and $CH_3OH$ as the methacrylate monomer and electrophile in 66% yield (GC yield). Yields were determined by GC analysis using an internal standard ($C_{12}H_{26}$). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 56% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.25-7.10 (m, 10H), 4.72 (sept, *J* = 6.0 Hz, 1H), 2.85 (dd, *J* = 13.6, 6.8 Hz, 1H), 2.19 (qud, *J* = 7.2, 3.2 Hz, 1H), 2.10-1.96 (m, 3H), 1.22-1.14 (m, 4H), 1.12 (d, *J* = 6.4 Hz, 6H), 1.07-0.95 (m, 1H), 0.92 (d, *J* = 7.2 Hz , 3H), 0.88-0.81 (m, 1H), 0.78 (t, *J* = 6.8 Hz, 3H); $^{13}$C NMR (100MHz, $CDCl_3$) δ 176.7, 148.4, 148.2, 128.3 (2C), 128.2 (2C), 127.9 (2C), 127.8 (2C), 125.7 (2C), 67.3, 49.7, 41.3, 38.0, 36.1, 32.6, 23.9, 22.6, 21.7, 20.4, 14.1 (2C). HRMS (ESI) *m/z* Calcd for $C_{25}H_{34}O_2Na$ $[M+Na]^+$ 389.2451; Found: 389.2446.




***tert*-Butyl 2-methyl-4,4-diphenylnonanoate :** Obtained from *tert*-butyl methacrylate and $CH_3OH$ as the methacrylate monomer and electrophile in 97% yield (GC yield). Yields were determined by GC analysis using an internal standard ($C_{12}H_{26}$). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 42% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.30-7.12 (m, 10H), 2.83 (dd, *J* = 14.4, 6.4 Hz, 1H), 2.13-2.06 (m, 1H), 2.04-1.99 (m, 2H), 1.94 (dd, *J* = 13.6, 3.6 Hz, 1H), 1.34 (s, 9H), 1.21-1.14 (m, 4H), 1.08-0.97 (m, 1H), 0.91-0.82 (m, 7H), 0.78 (t, *J* = 6.8 Hz, 3H); $^{13}$C NMR (100MHz, $CDCl_3$) δ 176.7, 148.6, 148.4, 128.3 (2C), 128.2 (2C), 127.9 (2C), 127.8 (2C), 125.7 (2C), 79.7, 49.8, 41.2, 38.1, 36.8, 32.6, 28.1 (3C), 23.9, 22.6, 20.5, 14.1. HRMS (ESI) *m/z* Calcd for $C_{26}H_{36}O_2Na$ $[M+Na]^+$ 403.2608; Found: 403.2599.

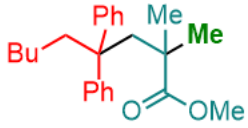



**Benzyl 2-methyl-4,4-diphenylnonanoate :** Obtained from benzyl methacrylate and $CH_3OH$ as the methacrylate monomer and electrophile in 76% yield (GC yield). Yields were determined by GC analysis using an internal standard ($C_{12}H_{26}$). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 56% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.38-7.12 (m, 15H), 4.76 (dd, *J* = 33.2, 12.6, Hz, 2H), 2.83 (dd, *J* = 14.4, 8.4 Hz, 1H), 2.35 (qud, *J* = 8.0, 2.8 Hz, 1H), 2.12-2.05 (m, 2H), 1.99 (td, *J* = 13.6, 4.4 Hz, 1H), 1.26-1.08 (m, 4H), 1.01 (d, *J* = 7.6 Hz , 3H), 1.00-0.81 (m, 2H), 0.78 (t, *J* = 6.8 Hz, 3H); $^{13}$C NMR (100MHz, $CDCl_3$) δ 176.9, 148.4, 148.0, 136.3, 128.6 (2C), 128.4 (2C), 128.2 (2C), 128.1 (2C), 128.0 (2C), 127.8 (2C), 125.8 (3C), 66.1, 49.6, 41.6, 38.1, 36.0, 32.6, 23.9, 22.6, 20.5, 14.2. HRMS (ESI) *m/z* Calcd for $C_{29}H_{34}O_2Na$ $[M+Na]^+$ 437.2451; Found: 437.2446.

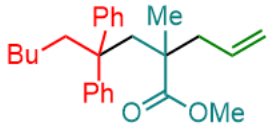



**2,2,2-Trifluoroethyl 2-methyl-4,4-diphenylnonanoate :** Obtained from 2, 2, 2- trifluoroethyl methacrylate and $CH_3OH$ as the methacrylate monomer and electrophile in 77% yield (GC yield). Yields were determined by GC analysis using an internal standard ($C_{12}H_{26}$). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 64% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.25-7.11 (m, 10H), 4.08 (dq, *J* = 12.4, 8.8 Hz, 1H), 3.95 (dq, *J* = 12.4, 8.0 Hz, 1H), 2.77 (dd, *J* = 14.4, 8.8 Hz, 1H), 2.48-2.40 (m, 1H), 2.18 (dd, *J* = 11.6, 2.8 Hz, 1H), 2.11 (dd, *J* = 11.6, 5.2 Hz, 1H), 2.00 (td, *J* = 11.6, 5.2 Hz, 1H), 1.24-1.13 (m, 4H), 1.06 (d, *J* = 6.8 Hz, 3H), 1.00-0.86 (m, 2H), 0.79 (t, *J* = 6.8 Hz, 3H); $^{13}$C NMR (100MHz, $CDCl_3$) δ 175.2, 148.1, 147.4, 128.5 (2C), 128.1 (2C), 128.0 (2C), 127.8 (2C), 125.9 (2C), 123.1 (q, *J* = 275 Hz, 1C), 60.2 (t, *J* = 3.6 Hz, 1C), 49.4, 41.5, 38.1, 35.7, 32.5, 23.8, 22.5, 20.3, 14.1; $^{19}$F NMR (376MHz, $CDCl_3$) δ -73.6 (s, 3F). HRMS (ESI) *m/z* Calcd for $C_{24}H_{29}O_2F_3Na$ $[M+Na]^+$

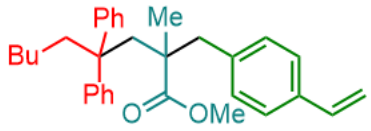
429.2012; Found: 429.2007.




**Methyl 2,2-dimethyl-4,4-diphenylnonanoate :** Obtained from methyl methacrylate and MeI as the methacrylate monomer and electrophile in 87% yield (GC yield). Yields were determined by GC analysis using an internal standard ($C_{12}H_{26}$). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 50% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.23-7.10 (m, 10H), 3.37 (s, 3H), 2.63 (s, 2H), 2.11-2.07 (m, 2H), 1.20-1.12 (m, 4H), 1.04-0.98 (m, 6H), 0.91-0.88 (m, 2H), 0.78 (t, *J* = 6.8 Hz, 3H); $^{13}$C NMR (100MHz, $CDCl_3$) δ 178.1, 148.9 (2C), 128.5 (4C), 127.6 (4C), 125.7 (2C), 51.6, 49.5, 47.5, 42.0, 38.1, 32.6, 27.8 (2C), 24.2, 22.6, 14.2. HRMS (ESI) *m/z* Calcd for $C_{24}H_{32}O_2Na$ $[M+Na]^+$ 375.2295; Found: 375.2286.

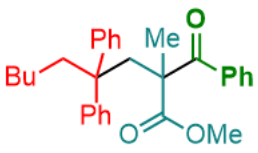



**Methyl 2-allyl-2-methyl-4,4-diphenylnonanoate :** By using the 100 cm R2 flow reactor, Obtained from methyl methacrylate and Allyl iodide as the methacrylate monomer and electrophile in 79% yield (GC yield). Yields were determined by GC analysis using an internal standard ($C_{12}H_{26}$). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 47% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.24-7.10 (m, 10H), 5.62-5.52 (m, 1H), 5.04-4.98 (m, 2H), 3.37 (s, 3H), 2.86 (d, *J* = 14.8 Hz, 1H), 2.44-2.38 (m, 2H), 2.22 (ddd, *J* = 13.2, 11.2, 5.6 Hz, 1H), 2.04 (dd, *J* = 13.6, 8.4 Hz, 1H), 1.94 (ddd, *J* = 13.2, 11.2, 4.8 Hz, 1H), 1.26-1.11 (m, 4H), 0.98-0.85 (m, 2H), 0.83 (s, 3H), 0.78 (t, *J* = 6.8 Hz, 3H); $^{13}$C NMR (100MHz, $CDCl_3$) δ 176.8, 149.5, 148.5, 133.7, 128.5 (2C), 128.4 (2C), 127.6 (4C), 125.7 (2C), 118.6, 51.4, 49.4, 47.8, 46.7, 45.7, 38.2, 32.5, 24.2, 22.6, 20.8, 14.1. HRMS (ESI) *m/z* Calcd for $C_{26}H_{34}O_2Na$ $[M+Na]^+$ 401.2451; Found: 401.2441.

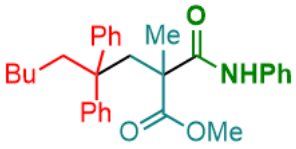



**Methyl 2-methyl-4,4-diphenyl-2-(4-vinylbenzyl)nonanoate :** Obtained from methyl methacrylate and 1-(iodomethyl)-4-vinylbenzene as the methacrylate monomer and electrophile in 87% yield (GC yield). Yields were determined by GC analysis using an internal standard ($C_{12}H_{26}$). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 59% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.25-7.06 (m, 12H), 6.97 (d, *J* = 7.6 Hz, 2H), 6.63 (dd, *J* = 17.2, 10.4 Hz, 1H), 5.66 (d, *J* = 17.6 Hz, 1H), 5.15 (d, *J* = 10.8 Hz, 1H), 3.31 (s, 3H), 3.07 (d, *J* = 13.6 Hz, 2H), 2.50 (dd, *J* = 23.2, 12.8 Hz, 2H), 2.28-2.21 (m, 1H), 1.96-1.89 (m, 1H), 1.19-1.09 (m, 4H), 0.92-0.83 (m, 2H), 0.79-0.74 (m, 6H); $^{13}$C NMR (100MHz, $CDCl_3$) δ 176.6, 149.5, 148.4, 136.9, 136.7, 136.1, 130.8 (2C), 128.6 (2C), 128.5 (2C), 127.8 (2C), 127.6 (2C), 125.9 (2C), 125.8 (2C), 113.5, 51.4, 49.6 (2C), 47.3 (2C), 38.4, 32.6, 24.3, 22.7, 20.2,

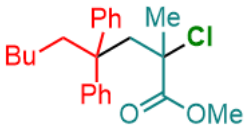
14.2. HRMS (ESI) *m/z* Calcd for $C_{32}H_{38}O_2Na$ $[M+Na]^+$ 477.2764; Found: 477.2752.




**Methyl 2-benzoyl-2-methyl-4,4-diphenylnonanoate :** Obtained from methyl methacrylate and PhCOCl as the methacrylate monomer and electrophile in 83% yield (GC yield). Yields were determined by GC analysis using an internal standard ($C_{12}H_{26}$). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 62% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 7.2 Hz, 2H), 7.44 (tt, *J* = 7.2, 1.2 Hz, 1H), 7.38-7.31 (m, 2H), 7.24-7.05 (m, 10H), 3.36 (s, 3H), 3.28-3.19 (m, 2H), 2.15-2.03 (m, 2H), 1.17 (s, 3H), 1.13-0.94 (m, 4H), 0.90-0.76 (m, 2H), 0.72 (t, *J* = 7.2 Hz, 3H); $^{13}$C NMR (100MHz, $CDCl_3$) δ 197.4, 175.1, 149.0 (2C), 135.7, 132.4, 128.4-127.7 (12C), 125.8 (2C), 56.9, 52.3, 48.7, 42.3, 38.0, 32.3, 24.3, 22.6, 21.6, 14.1. HRMS (ESI) *m/z* Calcd for $C_{30}H_{34}O_3Na$ $[M+Na]^+$ 465.2400; Found: 465.2396.




**Methyl 2-methyl-4,4-diphenyl-2-(phenylcarbamoyl)nonanoate :** Obtained from methyl methacrylate and PhNCO as the methacrylate monomer and electrophile. After the product solution was collected and stirred for 15 minutes, sat. $NH_4Cl$ aq. was added to the aliquot. Yields were determined in 93% yield by GC analysis using an internal standard ($C_{12}H_{26}$). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 73% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 10.30 (s, 1H), 7.61 (d, *J* = 7.2 Hz, 2H), 7.33 (t, *J* = 7.6 Hz, 2H), 7.25-7.05 (m, 11H), 3.36-3.25 (m, 1H), 3.22 (s, 3H), 2.84 (d, *J* = 13.6 Hz, 1H), 2.14-1.92 (m, 2H), 1.55 (s, 3H), 1.26-0.94 (m, 5H), 0.81-0.76 (m, 1H), 0.70 (t, *J* = 6.8 Hz, 3H); $^{13}$C NMR (100MHz, $CDCl_3$) δ 176.5, 169.6, 148.9, 147.1, 138.3, 129.5 (2C), 129.0 (2C), 128.2 (2C), 127.7 (2C), 127.5 (2C), 126.2, 125.8, 124.2, 119.9 (2C), 52.2, 50.9, 49.5, 46.5, 38.0, 32.4, 27.4, 24.1, 22.6, 14.2. HRMS (ESI) *m/z* Calcd for $C_{30}H_{35}O_3NNa$ $[M+Na]^+$ 480.2509; Found: 480.2490.

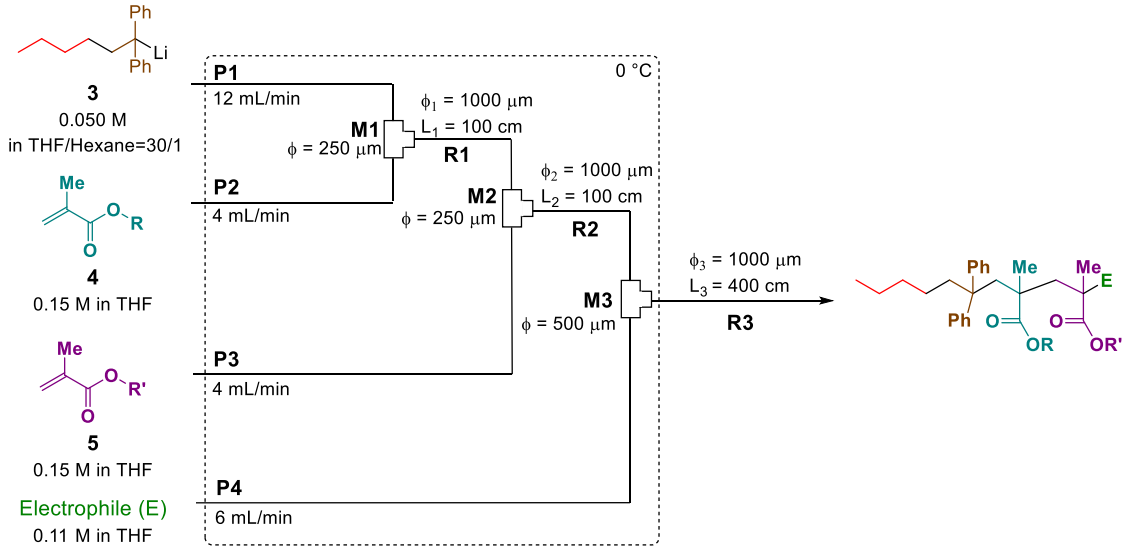



**Methyl 2-chloro-2-methyl-4,4-diphenylnonanoate :** Obtained from methyl methacrylate and $CCl_4$ as the methacrylate monomer and electrophile in 86% yield (GC yield). Yields were determined by GC analysis using an internal standard ($C_{12}H_{26}$). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 39% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.25-7.13 (m, 10H), 3.40 (s, 3H), 3.28 (d, *J* = 14.4 Hz, 1H), 3.04 (d, *J* = 14.8 Hz, 1H), 2.19 (t, *J* = 8.0 Hz, 2H), 1.51 (s, 3H), 1.22-1.16 (m, 4H), 1.02-0.93 (m, 2H), 0.78 (t, *J* = 6.4 Hz, 3H); $^{13}$C NMR (100MHz, $CDCl_3$) δ 171.3, 147.7, 147.6, 128.6, 128.4, 127.8 (6C), 126.1, 126.0,

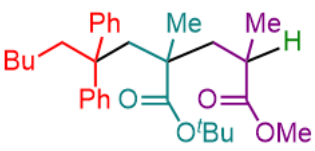
69.1, 52.9, 49.8, 48.7, 38.2, 32.4, 29.5, 24.1, 22.6, 14.1. HRMS (ESI) *m/z* Calcd for $C_{23}H_{29}O_2ClNa$ $[M+Na]^+$ 395.1748; Found: 395.1739.

### 2-5-5. Synthesis of Sequenced Oligomers Using Multiple Monomers.

#### 2-5-5-1. Synthesis of Multi-methacrylate and End-capping Functionalization.

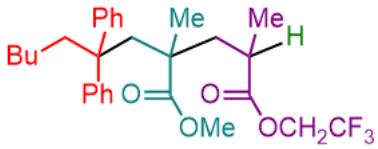



A flow microreactor system consisting of three T-shaped micromixers (**M1**, **M2**, and **M3**), three microtube reactors (**R1**, **R2**, and **R3**), and five pre-cooling units (**P1** (L = 100 cm), **P2** (50 cm), **P3** (50 cm), and **P4** (100 cm)) was used in a cooling bath at 0 °C. A solution of diphenylhexyl lithium (**3**, 0.050 M in THF/hexane=30/1, flow rate: 12 mL/min) and a solution of methacrylate monomer (**4**, 0.15 M in THF, flow rate: 4.0 mL/min) were introduced to **M1** ($\phi$ = 250 μm) using syringe pumps, and the mixture was passed through **R1** ($\phi$ = 1000 μm, 100 cm, residence time $t^{R1}$ = 3.0 s). The resulting solution was introduced to **M2** ($\phi$ = 250 μm), where a solution of methacrylate monomer (**5**, 0.15 M in THF, flow rate: 6.0 mL/min) was also introduced. The resulting solution was passed through **R2** ($\phi$ = 1000 μm, L = 100 cm, residence time = 2.4 s). The resulting solution was introduced to **M3** ($\phi$ = 500 μm), where a solution of electrophile (0.15 M in THF) was also introduced (flow rate: 6.0 mL/min). The resulting solution was passed through **R3** ($\phi$ = 1000 μm, L = 400 cm, residence time = 7.3 s). After a steady state was reached, the product solution was collected for 10 seconds. To the aliquot, sat. $NH_4Cl$ aq. was added, and then the organic phase was analyzed by GC and NMR.



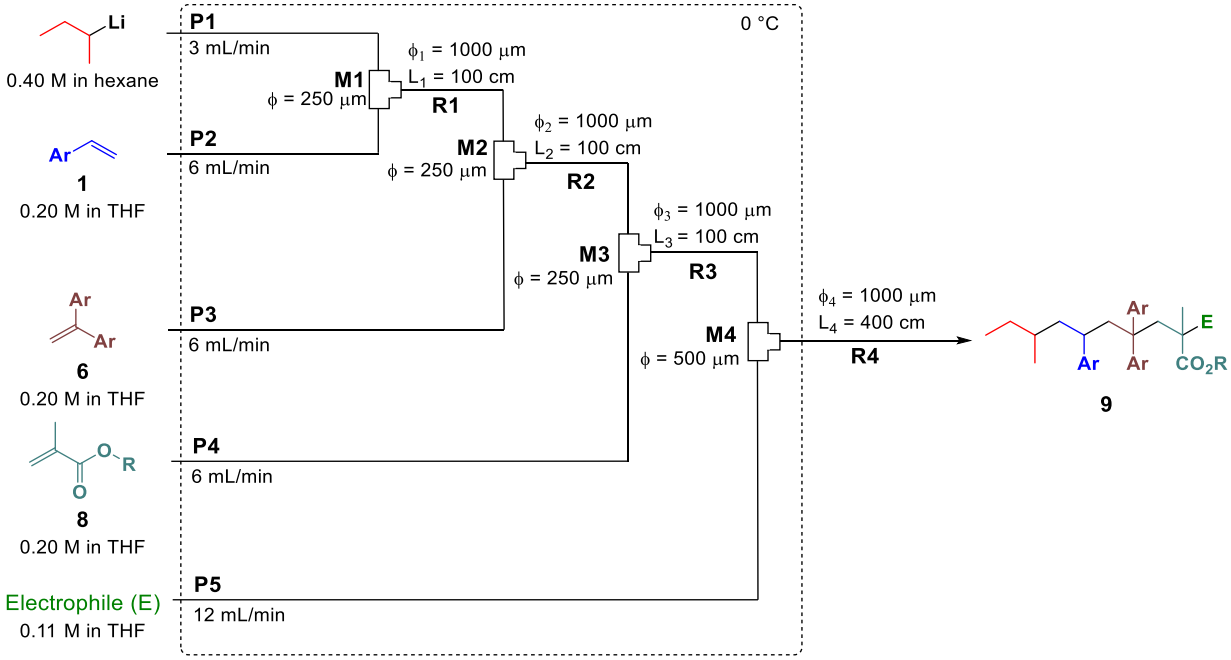

**1-(tert-butyl) 5-methyl 2-(2,2-diphenylheptyl)-2,4-dimethylpentanedioate :** Obtained from *tert*-butoxy methacrylate and methyl methacrylate as the methacrylate monomer **4** and **5** in

72% yield (NMR yield). Yields were determined by NMR analysis using an internal standard (1,1,2,2-tetrachloroethane). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 14% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$, diastereomer ratio = 75 :25) δ 7.27-7.11 (m, 10H), 3.61-3.58 (m, 3H), 2.91-2.80 (m, 1H), 2.49-2.41 (m, 0.75H), 2.31-2.23 (m, 1.25H), 2.22-2.08 (m, 1.75H), 2.05-1.95 (m, 1H), 1.80 (dd, *J* = 14.4, 9.2 Hz, 0.25H), 1.48-1.45 (m, 9.25H), 1.29-1.12 (m, 4.75H), 1.06-1.03 (m, 3H), 0.99-0.80 (m, 2H), 0.77-0.74 (m, 3H), 0.54-0.49 (m, 3H); $^{13}$C NMR (100MHz, $CDCl_3$, diastereomer ratio = 75 :25) δ 177.8 (1C), 176.5 (1C), 149.1-148.2 (2C), 129.1-127.6 (8C), 125.8-125.6 (2C), 80.7-80.6 (1C), 51.7 (1C), 50.2-50.1 (1C), 49.3-47.5 (1C), 46.8-46.4 (1C), 46.4-46.2 (1C), 37.5 (1C), 36.3-35.7 (1C), 32.5 (1C), 28.2-28.1 (3C), 24.9-24.8 (1C), 22.6 (1C), 21.5 (1C), 20.5-20.4 (1C), 14.1 (1C). HRMS (ESI) *m/z* Calcd for $C_{31}H_{44}O_4Na$ $[M]^+$ 503.3132; Found: 503.3122.

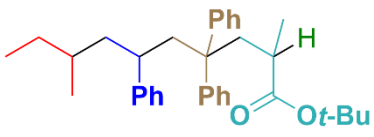



**1-methyl 5-(2,2,2-trifluoroethyl) 2-(2,2-diphenylheptyl)-2,4-dimethylpentanedioate :** Obtained from methyl methacrylate and 2,2,2-trifluoroethyl methacrylate as the methacrylate monomer **4** and **5** in 77% yield (GC yield). Yields were determined by GC analysis using an internal standard ($C_{12}H_{26}$). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 41% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$, diastereomer ratio = 85 :15) δ 7.25-7.10 (m, 10H), 4.48-4.30 (m, 2H), 3.39-3.35 (m, 3H), 2.83-2.77 (m, 1H), 2.53-2.46 (m, 1H), 2.44-2.40 (m, 1H), 2.36-2.27 (m, 1H), 2.23-2.15 (m, 1H), 2.00-1.89 (m, 1H), 1.32-1.25 (m, 1H), 1.23-1.03 (m, 7H), 0.97-0.76 (m, 8H); $^{13}$C NMR (100MHz, $CDCl_3$, diastereomer ratio = 85 :15) δ 176.7-176.6 (1C), 175.6-175.1 (1C), 149.1-148.2 (2C), 128.5-127.2 (8C), 125.7 (2C), 123.1 (d, *J* = 276 Hz, 1C), 60.4 (q, *J* = 36 Hz, 1C), 51.6-51.5 (1C), 49.5-49.4 (1C), 47.6-47.1 (1C), 46.2-45.7 (1C), 45.6-45.4 (1C), 38.2 (1C), 36.1-35.5 (1C), 32.5 (1C), 24.2-24.0 (1C), 22.6 (1C), 21.3-21.1 (1C), 20.1-19.5 (1C), 14.1 (1C). HRMS (ESI) *m/z* Calcd for $C_{29}H_{37}O_4F_3Na$ $[M]^+$ 529.2536; Found: 529.2532.

**2-5-5-2. Synthesis of an Adduct of styrene, diphenylethylene and Methacrylate and End-capping Functionalization.**

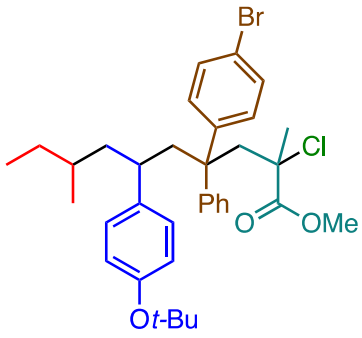



A flow microreactor system consisting of four T-shaped micromixers (**M1**, **M2**, **M3**, and **M4**), four microtube reactors (**R1**, **R2**, **R3**, and **R4**), and five pre-cooling units (**P1** (L = 50 cm), **P2** (100 cm), **P3** (100 cm), **P4** (100 cm), and **P5** (100 cm)) was used in a cooling bath at 0 °C. A solution of *s*-BuLi (0.40 M in hexane, flow rate: 3.0 mL/min) and a solution of styrene monomer (**1**, 0.20 M in THF, flow rate: 6.0 mL/min) were introduced to **M1** ($\phi$ = 250 μm) using syringe pumps, and the mixture was passed through **R1** ($\phi$ = 1000 μm, 100 cm, residence time $t^{R1}$ = 5.2 s). The resulting solution was introduced to **M2** ($\phi$ = 250 μm), where a solution of diphenyl ethylene monomer (0.20 M in THF) was also introduced (flow rate: 6.0 mL/min). The resulting solution was passed through **R2** ($\phi$ = 1000 μm, L = 100 cm, residence time = 3.1 s). The resulting solution was introduced to **M3** ($\phi$ = 250 μm), where a solution of methacrylate monomer (0.20 M in THF) was also introduced (flow rate: 6.0 mL/min). The resulting solution was passed through **R3** ($\phi$ = 1000 μm, L = 100 cm, residence time = 2.2 s). The resulting solution was introduced to **M4** ($\phi$ = 500 μm), where a solution of electrophile (0.11 M in THF) was also introduced (flow rate: 12.0 mL/min). The resulting solution was passed through **R4** ($\phi$ = 1000 μm, L = 400 cm, residence time = 5.7 s). After a steady state was reached, the product solution was collected for 30 seconds. To the aliquot, sat. $NH_4Cl$ aq. was added, and then the organic phase was analyzed by GC and NMR.

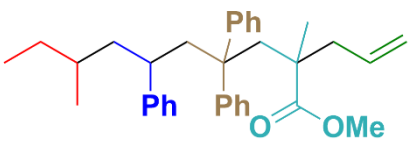



**tert-butyl 2,8-dimethyl-4,4,6-triphenyldecanoate :** Obtained from styrene, diphenyl ethylene, *tert*-butyl methacrylate, and methanol as styrene monomer, diphenyl ethylene monomer,

methacrylate monomer and electrophile reagent in 74% yield (NMR yield). Yields were determined by NMR analysis using an internal standard (1,1,2,2-tetrachloroethane). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 46% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$, diastereomer mixtures) δ 7.29-6.99 (m, 14H), 6.88-6.86 (m, 1H), 2.76-2.55 (m, 2H), 2.44-1.73 (m, 4H), 1.53-1.03 (m, 12H), 1.00-0.32 (m, 12H); $^{13}$C NMR (100MHz, $CDCl_3$, diastereomer mixtures) δ 176.2 (1C), 148.5-147.3 (3C), 128.9-127.7 (12C), 125.9-125.4 (3C), 79.5-79.3 (1C), 50.6-50.3 (1C), 47.8-45.6 (2C), 41.6-40.4 (1C), 39.3-39.1 (1C), 36.9 (1C), 31.4-31.3 (1C), 30.3-30.1 (1C), 28.0-27.8 (3C), 20.3-18.2 (2C), 11.1-10.7 (1C). HRMS (ESI) *m/z* Calcd for $C_{34}H_{44}O_2Na$ $[M+Na]^+$ 507.3234; Found: 507.3230.

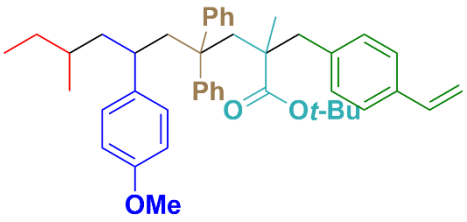



**methyl 4-(4-bromophenyl)-6-(4-(tert-butoxy)phenyl)-2-chloro-2,8-dimethyl-4-phenyldecanoate :** Obtained from 1-(tert-butoxy)-4-vinylbenzene, 1-bromo-4-(1-phenylvinyl)benzene, methyl methacrylate, and carbon tetrachloride as styrene monomer, diphenyl ethylene monomer, methacrylate monomer and electrophile reagent in 61% yield (NMR yield). Yields were determined by NMR analysis using an internal standard (1,1,2,2-tetrachloroethane). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 16% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$, diastereomer mixtures) δ 7.47-6.02 (m, 13H), 3.73-2.59 (m, 6H), 2.45-2.17 (m, 2H), 1.57-1.01 (m, 14H), 0.96-0.37 (m, 9H); $^{13}$C NMR (100MHz, $CDCl_3$, diastereomer mixtures) δ 171.3-170.9 (1C), 153.2 (1C), 147.2-146.6 (1C), 145.4-145.3 (1C), 142.2-142.1 (1C), 131.3-123.9 (13C), 120.4-120.2 (1C), 78.2-78.1 (1C), 68.7-68.5 (1C), 52.9-52.7 (1C), 50.6-50.3 (1C), 48.1-46.7 (3C), 39.0-38.5 (1C), 31.4-31.2 (1C), 30.2 (1C), 29.0 (3C), 28.6-27.7 (1C), 19.7-18.2 (1C), 11.6-10.6 (1C). HRMS (ESI) *m/z* Calcd for $C_{35}H_{44}O_3BrClNa$ $[M+Na]^+$ 649.2055; Found: 649.2053.



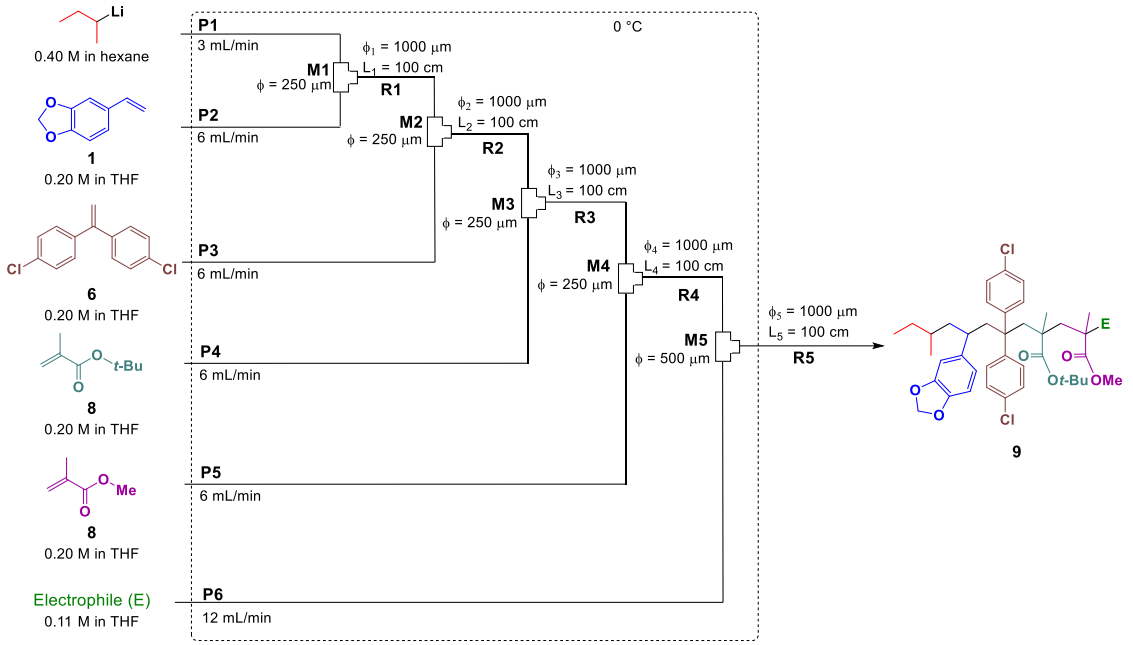

**methyl 2-allyl-2,8-dimethyl-4,4,6-triphenyldecanoat :** Obtained from styrene, diphenyl ethylene, methyl methacrylate, and allyl iodide as styrene monomer, diphenyl ethylene monomer, methacrylate monomer and electrophile reagent in 52% yield (NMR yield). Yields were determined by NMR analysis using an internal standard (dimethyl terephthalate). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 45% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$, diastereomer mixtures) δ 7.26-6.84 (m, 15H), 5.57-5.26 (m, 1H), 4.96-4.81 (m, 2H), 3.21-3.13 (m, 3H), 2.92-2.62 (m, 2H), 2.54-2.09 (m, 4H), 1.85-1.58 (m, 1H), 1.50-0.31 (m, 14H);

$^{13}$C NMR (100MHz, $CDCl_3$, diastereomer mixtures) δ 176.6-176.5 (1C), 149.8-146.7 (3C), 134.0-133.5 (1C), 129.6-125.3 (15C), 118.4-118.3 (1C), 51.4-45.5 (7C), 39.5-39.2 (1C), 31.2-30.3 (1C), 27.5-27.4 (1C), 21.9-17.9 (2C), 11.1-10.7 (1C). HRMS (ESI) *m/z* Calcd for $C_{34}H_{42}O_2Na$ $[M+Na]^+$ 505.3067; Found: 505.3077.

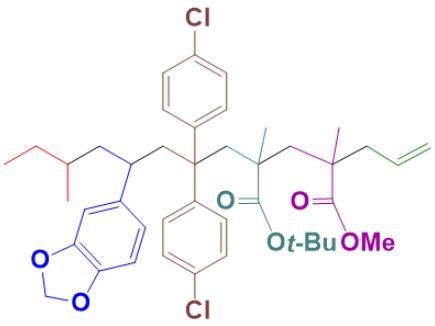



**tert-butyl 6-(4-methoxyphenyl)-2,8-dimethyl-4,4-diphenyl -2-(4-vinylbenzyl)decanoate :** Obtained from 1-methoxy-4-vinylbenzene, diphenyl ethylene, *tert*-butyl methacrylate, and allyl iodide as styrene monomer, diphenyl ethylene monomer, methacrylate monomer and electrophile reagent in 77% yield (NMR yield). Yields were determined by NMR analysis using an internal standard (1,1,2,2-tetrachloroethane). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 42% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$, diastereomer mixtures) δ 7.25-6.52 (m, 19H), 5.68 (d, $J$ = 18.0, 1H), 5.17 (d, $J$ = 10.8 Hz, 1H), 3.78-3.72 (m, 3H), 3.21-2.88 (m, 1H), 2.79-2.63 (m, 2H), 2.43-2.14 (m, 4H), 1.48-0.91 (m, 11H), 0.89-0.07 (m, 12H); $^{13}$C NMR (100MHz, $CDCl_3$, diastereomer mixtures) δ 176.7-176.3 (1C), 157.5-156.9 (1C), 148.3-147.3 (3C), 140.4-138.9 (1C), 137.2-135.8 (3C), 131.2-125.6 (16C), 113.7 (2C), 113.3-113.2 (1C), 80.5-80.4 (1C), 55.3 (1C), 52.1-45.9 (5C), 39.3-38.8 (1C), 31.4-30.5 (2C), 28.3-27.0 (3C), 20.3-19.9 (1C), 18.0-17.5 (1C), 11.3-10.8 (1C). HRMS (ESI) *m/z* Calcd for $C_{34}H_{42}O_2Na$ $[M+Na]^+$ 653.3965; Found: 653.3950.

### 2-5-5-3. Synthesis of an Adduct of styrene, diphenylethylene and Multiple Methacrylate and End-capping Functionalization.

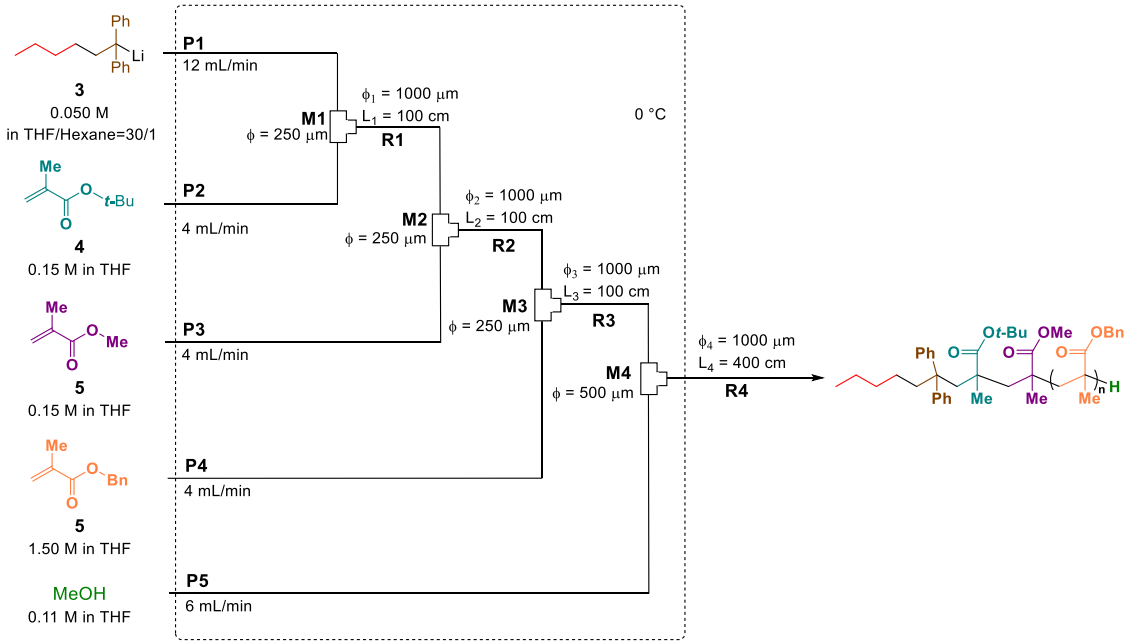



A flow microreactor system consisting of four T-shaped micromixers (**M1**, **M2**, **M3**, **M4**, and **M5**), five microtube reactors (**R1**, **R2**, **R3, R4**, and **R5**), and six pre-cooling units (**P1** (L = 50 cm), **P2** (100 cm), **P3** (100 cm), **P4** (100 cm), **P5** (100 cm), and **P6** (100 cm)) was used in a cooling bath at 0 °C. A solution of *s*-BuLi (0.40 M in hexane, flow rate: 3.0 mL/min) and a solution of 5-vinylbenzo[d][1,3]dioxole (**1**, 0.20 M in THF, flow rate: 6.0 mL/min) were introduced to **M1** ($\phi$ = 250 μm) using syringe pumps, and the mixture was passed through **R1** ($\phi$ = 1000 μm, 100 cm, residence time $t^{R1}$ = 5.2 s). The resulting solution was introduced to **M2** ($\phi$ = 250 μm), where a solution of 4,4'-(ethene-1,1-diyl)bis(chlorobenzene) (0.20 M in THF) was also introduced (flow rate: 6.0 mL/min). The resulting solution was passed through **R2** ($\phi$ = 1000 μm, L = 100 cm, residence time = 3.1 s). The resulting solution was introduced to **M3** ($\phi$ = 250 μm), where a solution of tert-butyl methacrylate (0.20 M in THF) was also introduced (flow rate: 6.0 mL/min). The resulting solution was passed through **R3** ($\phi$ = 1000 μm, L = 100 cm, residence time = 2.2 s). The resulting solution was introduced to **M4** ($\phi$ = 250 μm), where a solution of methyl methacrylate (0.20 M in THF) was also introduced (flow rate: 6.0 mL/min). The resulting solution was passed through **R4** ($\phi$ = 1000 μm, L = 100 cm, residence time = 1.7 s). The resulting solution was introduced to **M5** ($\phi$ = 500 μm), where a solution of electrophile (0.11 M in THF) was also introduced (flow rate: 12.0 mL/min). The resulting solution was passed through **R5** ($\phi$ = 1000 μm, L = 100 cm, residence time = 1.2 s). After a steady state was reached, the product solution was collected for 30 seconds. To the aliquot, sat. $NH_4Cl$ aq. was added, and then the organic phase was analyzed by NMR.



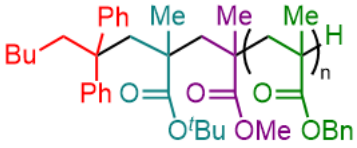

**5-(tert-butyl) 1-methyl 2-allyl-4-(4-(benzo[d][1,3]dioxol-5-yl)-2,2-bis(4-chlorophenyl)-6-methyloctyl)-2,4-dimethylpentanedioate :** Obtained from allyl iodide as the electrophile in 76% yield (NMR yield). Yields were determined by NMR analysis using an internal standard (1,1,2,2-tetrachloroethane). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 38% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$, diastereomer mixtures) δ 7.30-6.84 (m, 9H), 6.67-5.41 (m, 6H), 5.05-4.93 (m, 1H), 3.66-3.46 (m, 3H), 3.02-2.71 (m, 1H), 2.61-1.77 (m, 6H), 1.72-0.95 (m, 16H), 0.91-0.34 (m, 12H); $^{13}$C NMR (100MHz, $CDCl_3$, diastereomer mixtures) δ 177.6-175.8 (2C), 147.5-139.7 (5C), 134.1-134.0 (1C), 132.0-131.8 (2C), 131.0-130.0 (4C), 127.9-127.2 (4C), 121.0-120.1 (1C), 118.3-118.2 (1C), 108.1-107.6 (2C), 100.8-100.7 (1C), 81.0-80.7 (1C), 51.8-44.2 (8C), 40.0-39.3 (1C), 36.0-35.5 (1C), 31.2-29.8 (2C), 28.2-27.0 (3C), 23.2-19.9 (2C), 18.1-17.7 (1C), 11.3-10.7 (1C). HRMS (EI) *m/z* Calcd for $C_{43}H_{54}O_6Cl_2Na$ $[M+Na]^+$ 759.3190; Found: 759.3175.

### 2-5-5-4. Synthesis of an oligomer of methacrylate




A flow microreactor system consisting of four T-shaped micromixers (**M1**, **M2**, **M3**, and **M4**), four microtube reactors (**R1**, **R2**, **R3**, and **R4**), and five pre-cooling units (**P1** (L = 100 cm), **P2** (100 cm), **P3** (100 cm), **P4** (100 cm), and **P5** (100 cm)) was used in a cooling bath at 0 °C. A solution of diphenylhexyl lithium (**3**, 0.050 M in THF/hexane=30/1, flow rate: 12 mL/min) and a

solution of *tert*-butyl methacrylate (**1**, 0.15 M in THF, flow rate: 4.0 mL/min) were introduced to **M1** ($\phi$ = 250 μm) using syringe pumps, and the mixture was passed through **R1** ($\phi$ = 1000 μm, 100 cm, residence time $t^{R1}$ = 2.9 s). The resulting solution was introduced to **M2** ($\phi$ = 250 μm), where a solution of methyl methacrylate (0.15 M in THF) was also introduced (flow rate: 4.0 mL/min). The resulting solution was passed through **R2** ($\phi$ = 1000 μm, L = 100 cm, residence time = 2.4 s). The resulting solution was introduced to **M3** ($\phi$ = 250 μm), where a benzyl methacrylate (0.15 M in THF) was also introduced (flow rate: 4.0 mL/min). The resulting solution was passed through **R3** ($\phi$ = 1000 μm, L = 100 cm, residence time = 2.0 s). The resulting solution was introduced to **M4** ($\phi$ = 500 μm), where a solution of methanol (0.11 M in THF) was also introduced (flow rate: 6.0 mL/min). The resulting solution was passed through **R4** ($\phi$ = 1000 μm, L = 400 cm, residence time = 6.3 s). After a steady state was reached, the product solution was collected for 30 seconds. To the aliquot, sat. $NH_4Cl$ aq. was added, and then the organic phase was analyzed by NMR.




**sequence oligomer 41:** The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.62-6.94 (m, 58H), 5.19-4.66 (m, 20H), 3.71-3.40 (m, 3H), 2.82-0.38 (m, 79H). GPC *M*n: 2.8 × 103, PDI:1.18. MALDI-TOF-MS

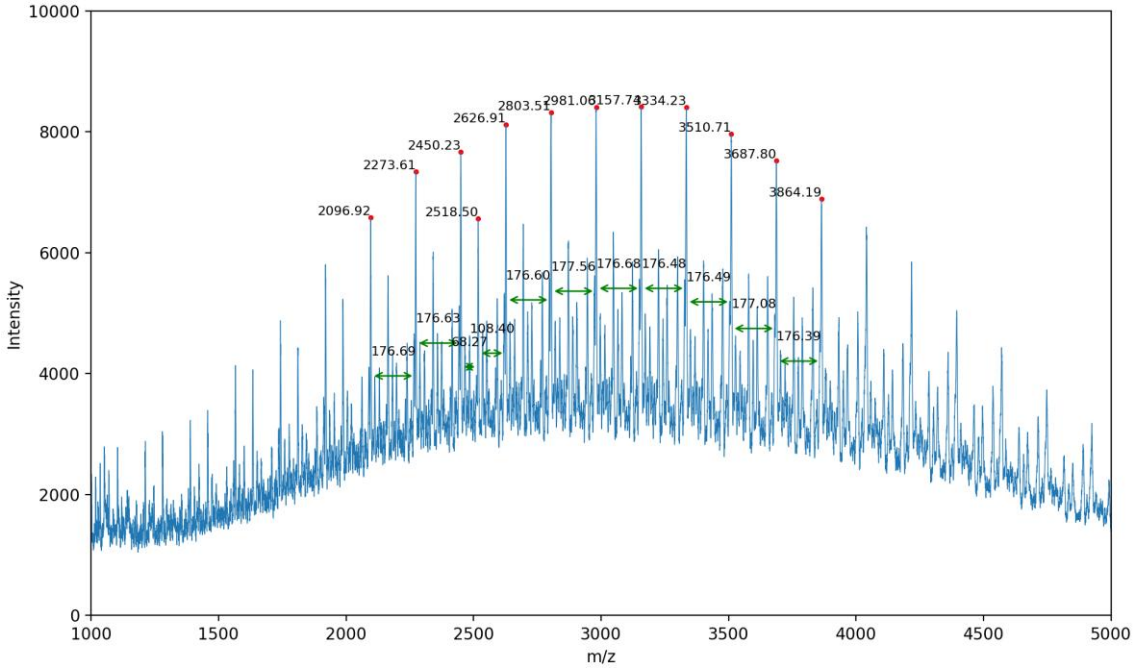
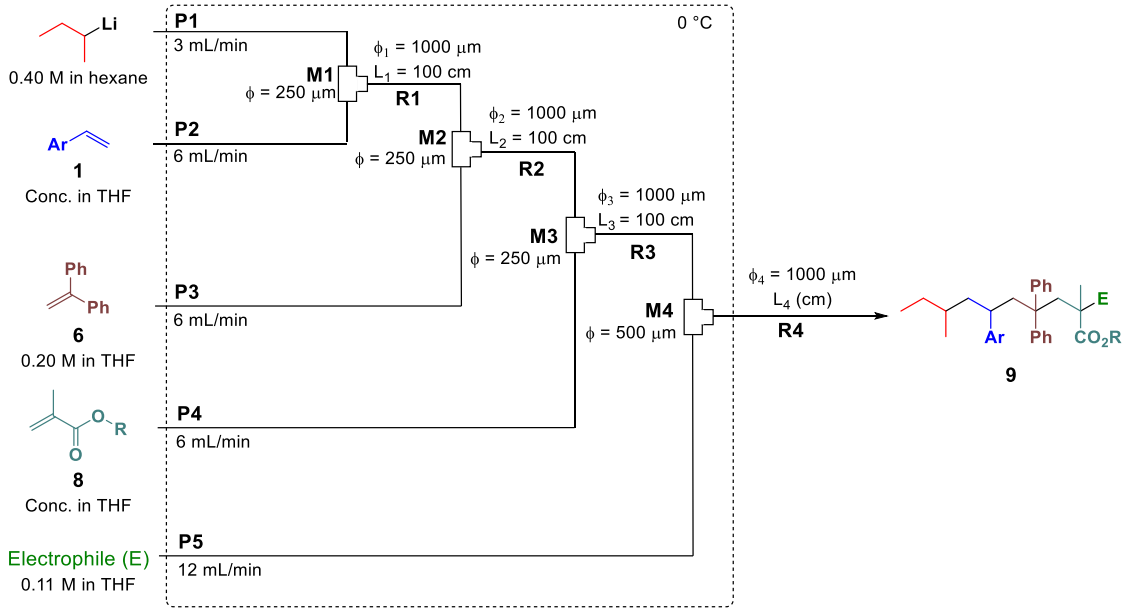
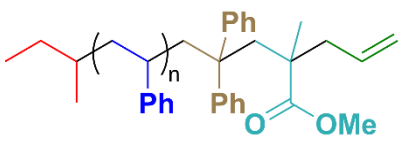



**Figure 7.** MALDI-TOF-MS spectrum for oligomer **41**. Polymer: 2 mg/mL, matrix: dihydroxybenzoic acid, trans-3-indoleacrylic acid (15-20 mg/mL), matrix : polymer = 5 : 1 (v/v)

### 2-5-5-5. Synthesis of oligomers composed of styrenes and methacrylates with end-capping functionalization.




A flow microreactor system consisting of four T-shaped micromixers (**M1**, **M2**, **M3**, and **M4**), four microtube reactors (**R1**, **R2**, **R3**, and **R4**), and five pre-cooling units (**P1** (L = 50 cm), **P2** (100 cm), **P3** (100 cm), **P4** (100 cm), and **P5** (100 cm)) was used in a cooling bath at 0 °C. A solution of *s*-BuLi (0.40 M in hexane, flow rate: 3.0 mL/min) and a solution of styrene monomer (**1**, Conc. in THF, flow rate: 6.0 mL/min) were introduced to **M1** ($\phi$ = 250 μm) using syringe pumps, and the mixture was passed through **R1** ($\phi$ = 1000 μm, 100 cm, residence time $t^{R1}$ = 5.2 s). The resulting solution was introduced to **M2** ($\phi$ = 250 μm), where a solution of diphenyl ethylene (0.20 M in THF) was also introduced (flow rate: 6.0 mL/min). The resulting solution was passed through **R2** ($\phi$ = 1000 μm, L = 100 cm, residence time = 3.1 s). The resulting solution was introduced to **M3** ($\phi$ = 250 μm), where a solution of methacrylate monomer (Conc. in THF) was also introduced (flow rate: 6.0 mL/min). The resulting solution was passed through **R3** ($\phi$ = 1000 μm, L = 100 cm, residence time = 2.2 s). The resulting solution was introduced to **M4** ($\phi$ = 500 μm), where a solution of electrophile (0.11 M in THF) was also introduced (flow rate: 12.0 mL/min). The resulting solution was passed through **R4** ($\phi$ = 1000 μm, $L_4$, residence time = 5.7 s). After a steady state was reached, the product solution was collected for 30 seconds. To the aliquot, sat. $NH_4Cl$ aq. was added, and then the organic phase was analyzed by NMR.




**sequence oligomer 44:** Obtained from styrene (conc.: 3.0 M), methyl methacrylate (conc.: 0.2 M), and allyl iodide as the styrene monomer, methyl methacrylate, and electrophile. The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$). 1H NMR (400 MHz, $CDCl_3$) δ 7.67-6.13 (m, 97H), 5.45-5.23 (m, 1H), 4.95-4.75 (m, 2H), 3.13-3.01 (m, 3H), 2.93-0.55 (m, 73H). GPC *M*n: 2.0 × $10^3$, PDI:1.14.

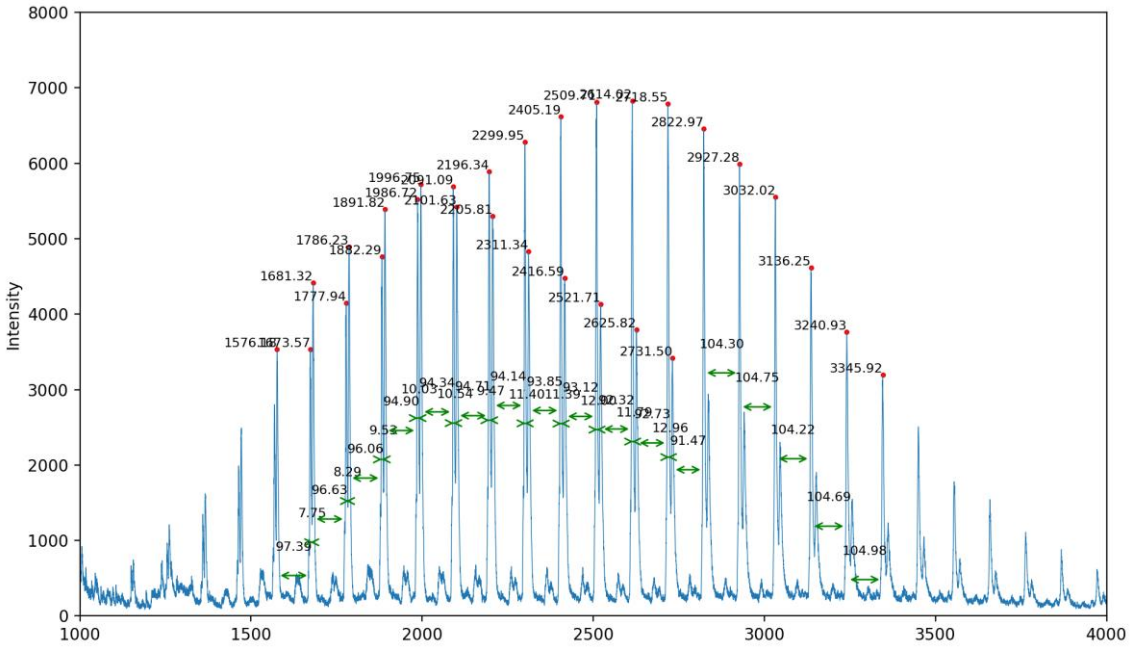
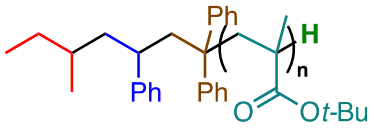



**Figure 8.** MALDI-TOF-MS spectrum for oligomer **44**. Polymer: 5 mg/mL, matrix: DCTB (40 mg/mL) salt: KTFA, AgTFA (5 mg/mL), matrix : salt : polymer = 4 : 1 : 4 (v/v).




**sequence oligomers 45-48:** Obtained from styrene (conc.: 0.2 M), tert-butyl methacrylate (conc.: 2.6 M), and methanol as the styrene monomer, methyl methacrylate, and electrophile. The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.42-6.95 (m, 15H), 3.04-0.08 (m, 241H). GPC *M*n: 2.2 × $10^3$, PDI:1.27.

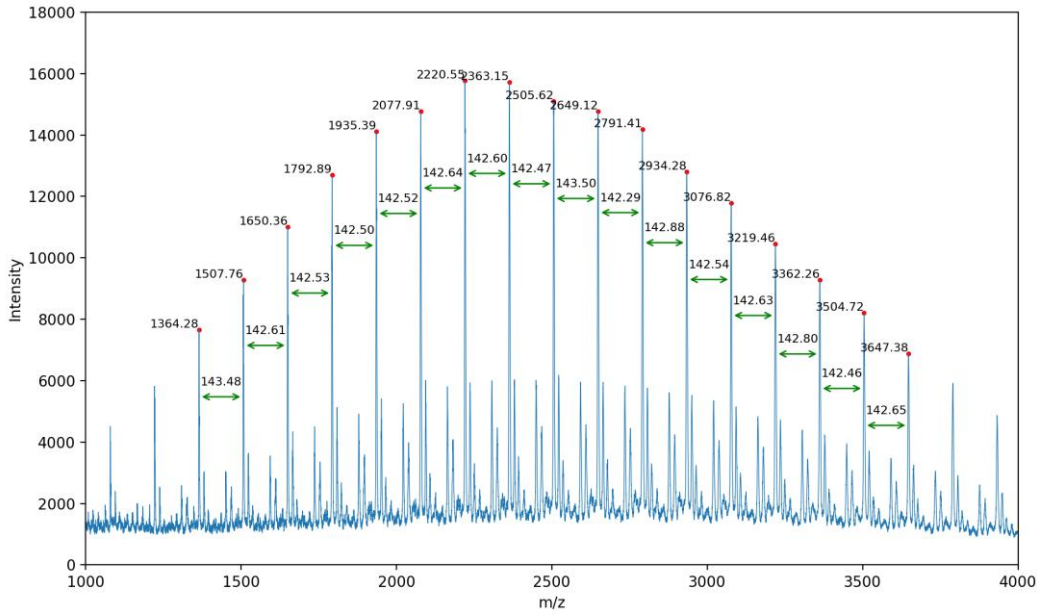
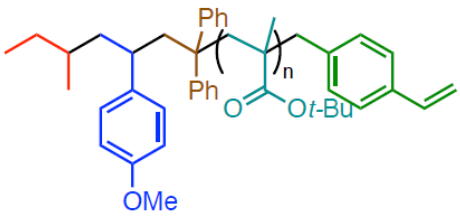



**Figure 9.** MALDI-TOF-MS spectrum for oligomer **48**. Polymer: 2 mg/mL, matrix: dihydroxybenzoic acid, trans-3-indoleacrylic acid, matrix : polymer = 5 : 1 (v/v).




**sequence oligomer 50:** Obtained from 1-methoxy-4-vinylbenzene (conc.: 0.2 M), tert-butyl methacrylate (conc.: 2.0 M), and 1- (iodomethyl)-4-vinylbenzene as the styrene monomer, methyl methacrylate, and electrophile. The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.34-6.51 (m, 19H), 5.73-5.65 (m, 1H), 5.20-5.18 (m, 1H), 3.80-3.67 (m, 3H), 3.18-0.07 (m, 163H). GPC *M*n: 2.0 × $10^3$, PDI:1.15.

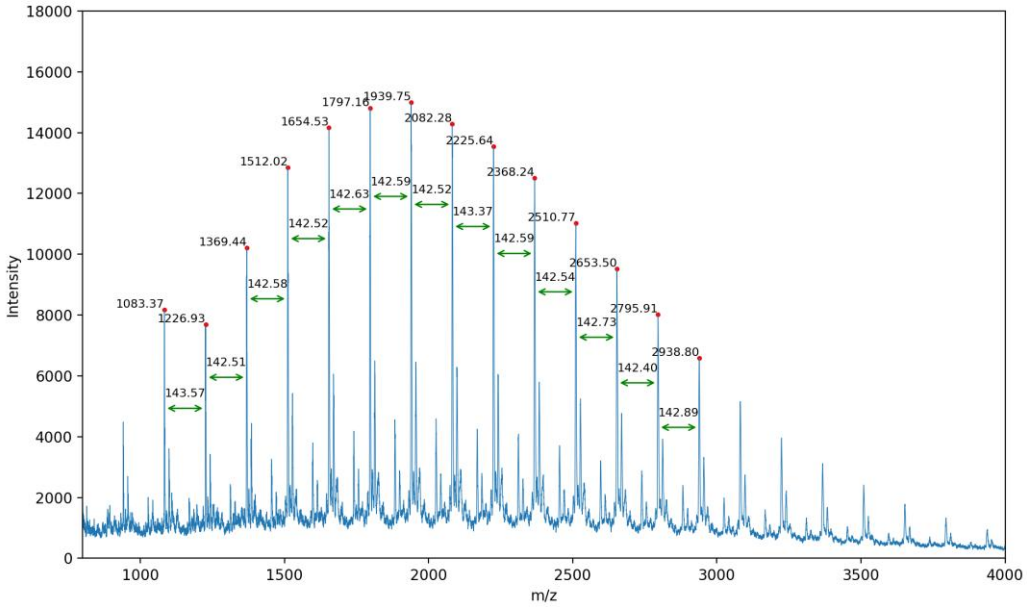



**Figure 10.** MALDI-TOF-MS spectrum for oligomer **50**. Polymer: 2 mg/mL, matrix: dihydroxybenzoic acid, trans-3- indoleacrylic acid (15-20 mg/mL), matrix : polymer = 5 : 1 (v/v).

# Chapter 3

# Flow-Controlled Living Anionic Monoadditional Reaction Initiated by Flash-Generated Benzophenone Dianions

## 3-1. Introduction

The discovery of macromolecules and the development of synthetic polymers based on polymerization techniques have revolutionized materials science and modern life, establishing polymers as indispensable materials across petrochemical, biomedical, and electronic industries. Among various polymerization techniques, living polymerization methods are considered to be among the most valuable methods, enabling the synthesis of structurally well-defined polymers characterized by narrow molecular weight distributions [1]. Such structurally well-defined polymers have recently found broad applications in high-impact research areas such as structure–property relationship studies [2], self-assembly [3], and reversible controlled polymerizations [4]. In these active research areas, anionic living polymerization has been regarded as one of the most powerful and versatile methodologies. The anionic chain ends remain living even in the absence of a capping agent, allowing their utilization in end-functionalization reactions with various electrophiles and for block copolymer synthesis [5].

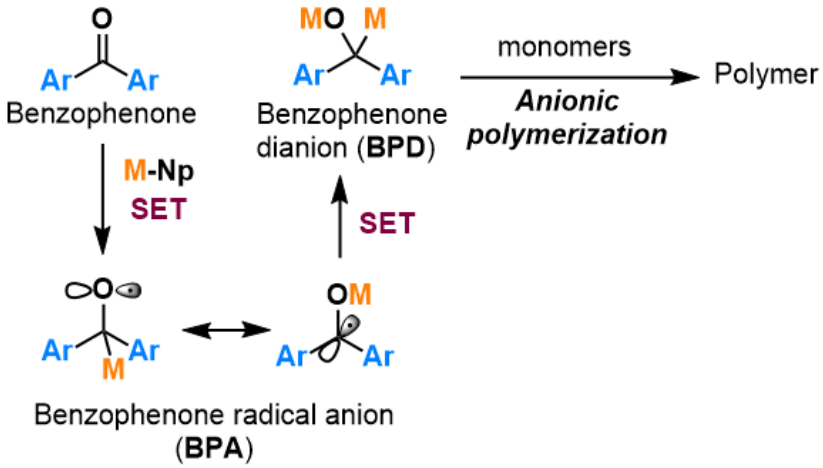
In our previous studies, the author reported a flow-controlled anionic polymerization whose characteristics include precise residence-time control, excellent heat-transfer efficiency, and rapid mixing under flow conditions [6, 7]. This approach is particularly attractive as it can be conducted under milder temperature conditions, in contrast to macro-batch systems where the cryogenic temperatures are typically required [8]. Recently, the author has also reported the selective monoaddition of polymerizable monomers under anionic polymerization conditions as an application of structurally well-defined polymers. This method enables precise sequence control in polymer synthesis and leads to the successful synthesis of sequence-defined oligomers [9]. In addition, by precisely controlling the residence time in flow, unstable functional organolithium anionic initiators from various functionalized halide compounds can be selectively generated and utilized for living anionic polymerization, ultimately leading to the successful synthesis of heterotelechelic polymers [10].

In contrast, a benzophenone radical anion (BPA), generated by reducing benzophenone [11], has been reported to work as an initiator for the anionic polymerization of methyl methacrylate (MMA) (Scheme 1) [12]. In addition, the electrons from the benzophenone dianion (BPD), formed via disproportionation of BPA [13], are thought to transfer to the monomer to promote polymerization [14]. The formation of BPD can be verified by a color change from blue to violet

upon addition of an excess reductant [15]. However, the selective generation of BPA or BPD has been challenging, thus limiting detailed studies on their reactivity [16].

Herein, the author reports the selective generation of benzophenone dianions as initiators for living anionic polymerization involving the monoaddition of methacrylates. The author describes the present flow microreactor method, which provides a versatile synthetic platform for anionic monoadditions and anionic polymerizations initiated by benzophenone dianions.

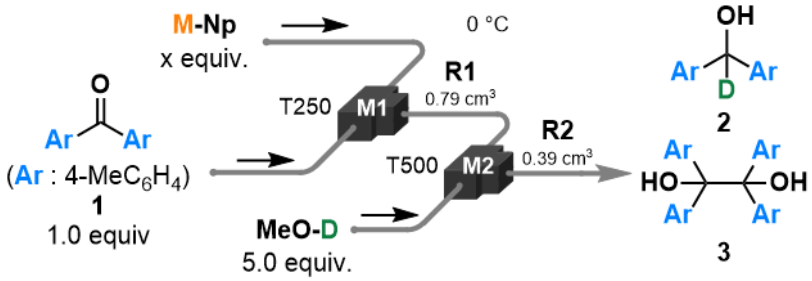
**Scheme 1.** Anionic polymerization of metal benzophenone dianions (BPDs) via single-electron transfer from benzophenone.



## 3-2. Results and Discussions

As an initial attempt, the author investigated the quantitative generation of benzophenone radical anion (BPA) and benzophenone dianion (BPD) under flash microflow conditions (Table 1). Although the generation of BPA proceeds readily, the subsequent two-electron reduction to BPD requires a much stronger reducing agent [17]. Strong reductants, MNp (M = Li, K), significantly influence both the reduction potential and the stability of the generated BPA and BPD species. Moreover, it is essential to precisely control the stoichiometric ratio between benzophenone derivatives and various metal naphthalenide reagents to achieve selective and quantitative generation of the desired active species. A microflow reactor equipped with a T-shaped mixer **M1** (inner diameter ($\varnothing_{I.D.}$): 250 μm) was employed to facilitate the rapid reaction between the MNp and the benzophenone derivative (**1**) at 0 °C, followed by a T-shaped mixer **M2** ($\varnothing_{I.D.}$: 500 μm) to quench the reaction with MeOD, thereby enabling the examination of the protonation of the anionic species (*see* Supporting Information for details).

**Table 1**. Investigations for generation of BPA and BPD in a microflow reactor system.[a]



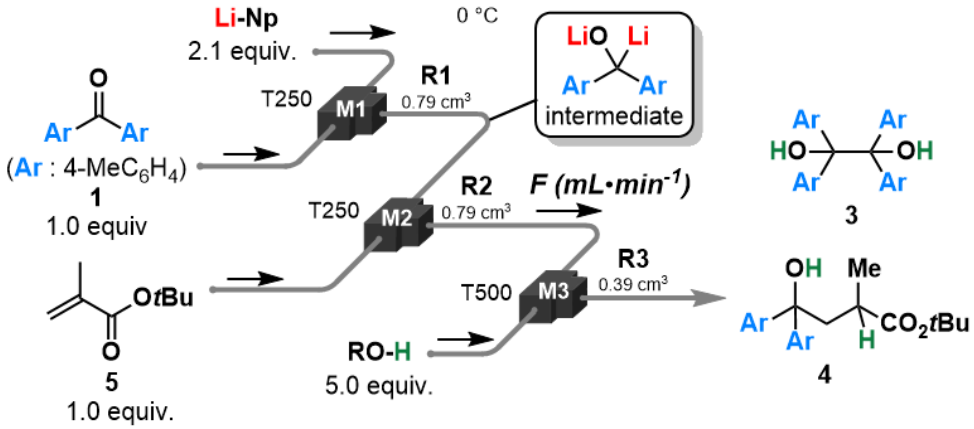

| Entry | Metal (**M**)[a] | equiv. (**x**) | **1** Conv. (%)[b] | Yield (%)[b] **2** | **3** |
|---|---|---|---|---|---|
| 1 | K | 1.0 | 58 | 22 (93) | 33 |
| 2 | | 2.0 | 83 | 75 (94) | 3 |
| 3 | | 2.6 | 100 | 97 (96) | - |
| 4 | Li | 1.0 | 88 | - | 83 |
| 5 | | 1.1 | 100 | 4 (99) | 92 |
| 6 | | 2.0 | 100 | 82 (98) | 16 |
| 7 | | 2.1 | 100 | 100 (100) | - |

[a] Residence times of **R1** and **R2** ($t^{R1}$, $t^{R2}$): *see* Supporting Information for details. [b] To a solution of naphthalene (2.3 equiv.) in THF, the metal was added at room temperature, and the

mixture was stirred for 2 h. [c] Yields were determined by $^{1}$H NMR analysis using an internal standard (dimethyl terephthalate).

To investigate the formation of BPA, **1** was reacted with 1.0 equivalent of potassium naphthalenide (KNp). Under these conditions, 58% of **1** was consumed, affording alcohol (**2**), derived from the reaction of BPD with MeOD, in 22% yield (93% D), along with diol (**3**), formed via dimerization of two BPAs in 33% yield (Entry 1). When 2.0 equivalents of KNp were used, it was not sufficient for the complete consumption of **1** and selective generation of BPD (Entry 2). However, employing 2.6 equivalents of KNp afforded **2** in 97% yield (96% D) (Entry 3). These results indicate that quantitative generation of BPA and BPD using KNp cannot be effectively achieved. Therefore, to enhance the reduction, lithium naphthalenide (LiNp), instead of KNp, was utilized. When 1.0 equivalent of LiNp was used, **3** was obtained in 83% yield (Entry 4). In contrast, using 1.1 equivalents of LiNp resulted in complete consumption of **1**, yielding **3** in 92% yield selectively (Entry 5). Subsequently, the generation of BPD was evaluated using 2.0 equivalents of LiNp. Under these conditions, **1** was completely consumed, affording **2** in 82% yield (98% D), along with **3** in 16% yield (Entry 6). When the amount of LiNp was slightly increased to 2.1 equivalents, the desired **2** was obtained quantitatively (100% D) (Entry 7). These findings demonstrate that the efficient use of LiNp promotes the generation of BPA and BPD from benzophenone derivatives.

**Table 2**. Investigations for monoaddition of lithium BPD with *tert*-butyl methacrylate in a microflow reactor system.[a]




| | | | yield (%)[a] | |
|---|---|---|---|---|
| Entry | **RO-H** | **F (mL·min$^{-1}$)** | **Chain (4)** | **3** |
| 1 | MeO-H | 6.0 | 65 | 9 |
| 2 | | 9.0 | 80 | 2 |

| | | | | |
|---|---|---|---|---|
| 3 | | 12.0 | 82 | - |
| 4 | | 15.0 | 96 | - |
| 5 | AcO-H | | 89 | - |

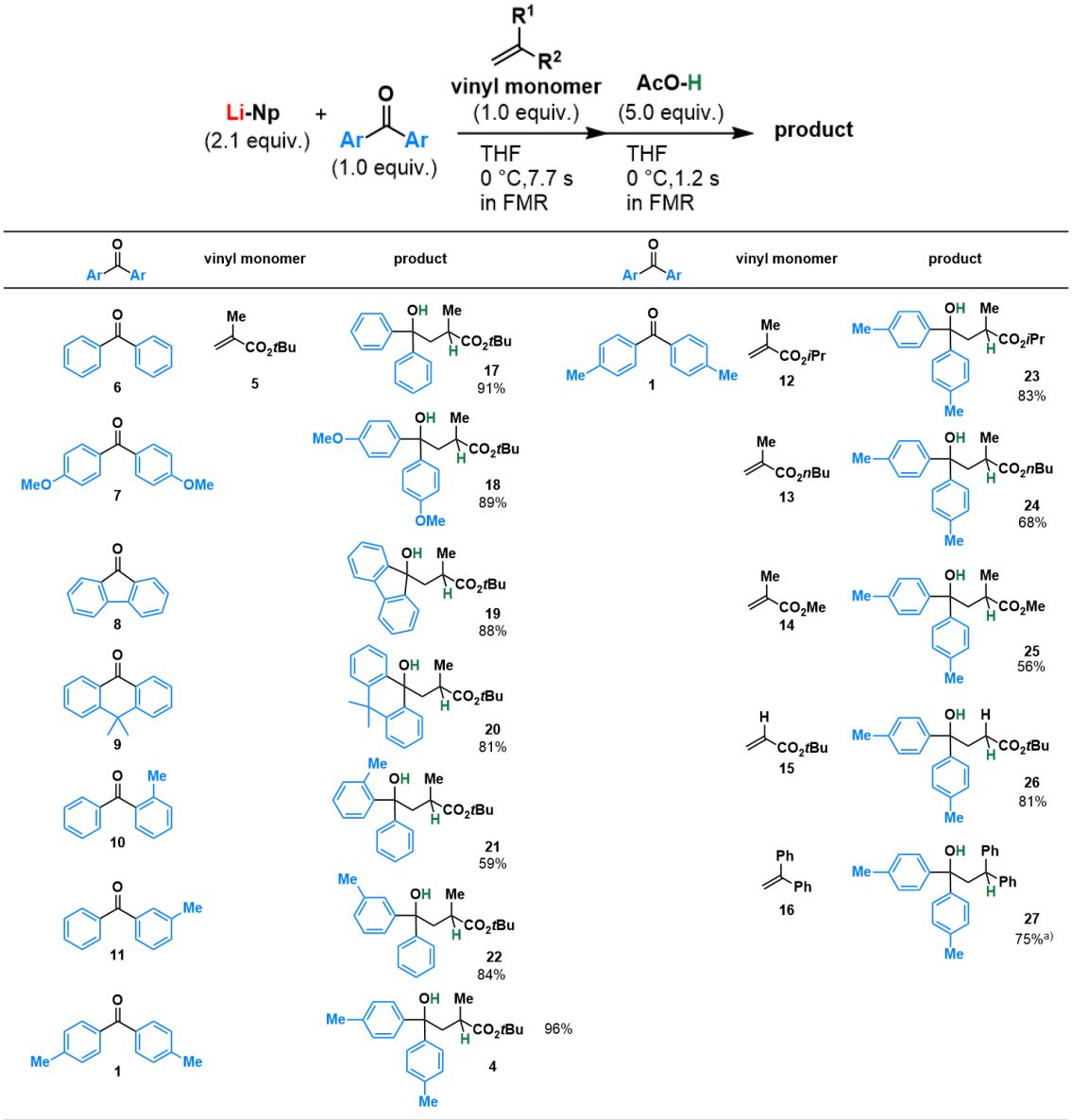
[a] Residence times of **R1**, **R2** and **R3** ($t^{R1}$, $t^{R2}$, $t^{R3}$): *see* Supporting Information for details. [b] Yields were determined by $^{1}$H NMR analysis using an internal standard (dimethyl terephthalate).

The author next investigated the anionic addition reaction between the generated lithium BPD and a vinyl monomer at a 1:1 molar ratio under microflow reactor conditions. Under the optimized conditions for generating the lithium BPD in the microflow reactor, the lithium BPD was continuously introduced into tert-butyl methacrylate **5** through a T-shaped mixer **M2** ($\varnothing_{I.D.}$: 250 μm) to promote rapid reaction, followed by quenching with an alcohol to terminate the process (Table 2). When MeOH was used as the quenching reagent at a flow rate of 6.0 mL·min$^{-1}$, the monoadduct **4** was selectively obtained in 65% yield, along with a small amount (9%) of the byproduct **3** (Entry 1). Subsequent experiments were conducted at higher flow rates (9.0–15.0 mL·min$^{-1}$) under identical conditions (Entries 2–4). As a result, the monoadduct **4** was obtained in the highest yield (96%) at 15.0 mL·min$^{-1}$, and no byproduct **3** was observed (Entry 4). However, when MeOH was used for quenching, the basic reagent MeOLi generated remained in the reaction mixture, which occasionally led to decomposition of the monoadduct **4** depending on the substrate structure (*see* Supporting Information for details). Therefore, HOAc was employed as an alternative quenching reagent to generate the less basic AcOLi under the same reaction conditions. Consequently, the monoadduct was obtained with high selectivity (89%), and decomposition-derived byproducts were effectively suppressed (Entry 5).

Using the optimized flash synthesis system, a selective anionic monoaddition reaction between lithium BPD species, generated from benzophenone derivatives and LiNp under stoichiometric conditions, and vinyl monomers was achieved. Subsequent precise quenching allowed for the synthesis of a chain-type monoadduct (Table 3). This reaction is not limited to di-p-tolylmethanone (**1**), but can also be applied to various benzophenone derivatives bearing different substituents, through a selective monoaddition reaction with *tert*-butyl methacrylate (**5**) as the vinyl monomer. In the reaction using general benzophenone (**6**), the corresponding monoadduct **17** was obtained in high yield with good selectivity. Furthermore, when a benzophenone derivative containing a methoxy group (**7**)—typically labile under reductive conditions—was used, the selective anionic monoaddition proceeded smoothly to afford the monoadduct **18** in high yield. In addition, when fluorenone (**8**) and anthracenone derivatives (**9**) were employed, the corresponding lithium BPD species were successfully generated and subjected to monoaddition reactions to afford monoadducts **19** and **20** in 88% and 81% yields, respectively. Finally, with benzophenone derivatives bearing methyl groups at the ortho (**10**) or meta (**11**) positions, the

corresponding lithium BPD species were successfully generated, affording monoadducts **21** and **22** in yields of 59% and 84%, respectively. These results indicate that this reaction system is scarcely affected by substituents.

**Table 3**. Scope of various vinyl monomers and benzophenone derivatives for flow monoaddition reactions using lithium dianionic species.

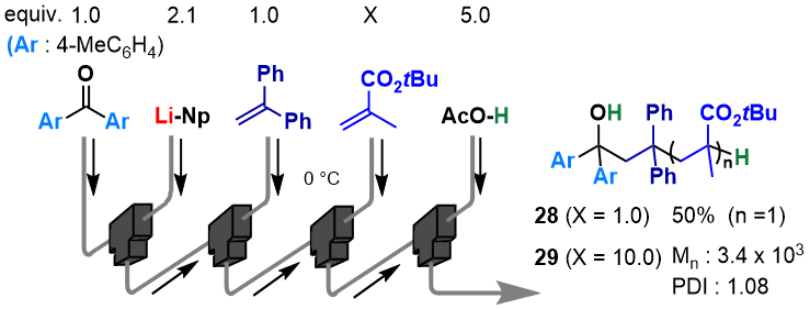



Yields were determined by $^{1}$H NMR analysis using an internal standard (dimethyl terephthalate). [a] Residence time: 24.7 s; recovered diphenylethylene (**16**): 17%.

*tert*-butyl (**5**), isopropyl (**12**), *n*-butyl (**13**), and methyl methacrylate (**14**) were employed as substrates for the anionic monoaddition to form the corresponding monoadducts **4**, **23**, **24**, and **25**

in yields of 96%, 83%, 68%, and 56%, respectively. These results suggest that, although the reaction system predominantly yields the monoadducts, monoaddition selectivity decreases depending on the substituents on the methacrylates, leading to the formation of cyclic by-products in increasing yields, from 0% (*tert*-butyl methacrylate) to 2% (isopropyl), 7% (*n*-butyl), and 17% (methyl methacrylate). In the case of *tert*-butyl acrylate (**15**), which features a hydrogen atom at the β-carbon, a selective monoaddition was expected to be challenging. Nevertheless, the corresponding monoadduct **26** was obtained in 81% yield. Furthermore, for diphenylethylene (**16**), which contains a phenyl group at the β-carbon, a slower reaction rate was anticipated. The longer residence time of 24.7 s resulted in monoadduct **27** in 75% yield, with 17% of diphenylethylene **16** recovered.

**Scheme 2**. Multi-component coupling sequence from different vinyl monomers

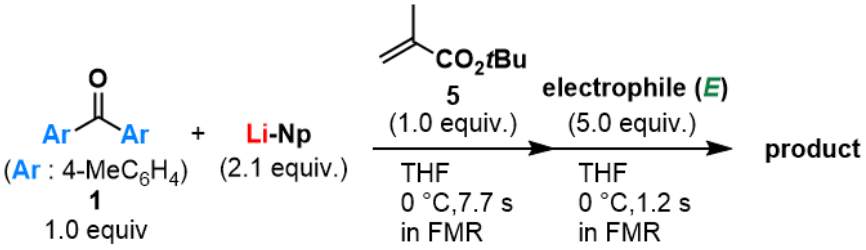


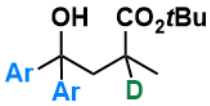
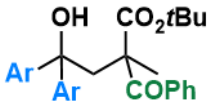
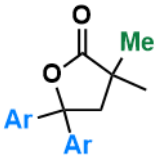
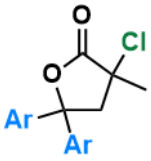

Since various compounds can be synthesized by introducing electrophiles or vinyl monomers into the monoaddition intermediate, vinyl monomers can be introduced in a one-to-one correspondence using the living anionic terminus. In addition, upon the addition of an excess monomer, polymerization can be induced. This approach enables the construction of well-defined linear sequences using initiators bearing diverse functional groups. After generating lithium BPD, two different diphenylethylene units and *tert*-butyl methacrylate were sequentially introduced at 1.0 equivalent, followed by protonation with acetic acid to terminate the reaction, yielding the multi-component coupling sequence compound 28 in moderate yield. Furthermore, when *tert*-butyl methacrylate was introduced in excess (10.0 equivalents), a sequence-ordered oligomer **29** ($M_n$: 3.4 × $10^3$, PDI: 1.08) was obtained (Scheme 2). These results demonstrate that substituents with distinct physical properties are present at both termini of the molecule, highlighting the utility of the sequence-defined synthesis.

End-capping reactions at living anionic termini are an important approach for the synthesis of functional polymers. In this study, the author investigated the selective introduction of electrophiles into the living anionic termini of monoadducts by reacting lithium BPD with *tert*-butyl methacrylate **5** in a 1:1 molar ratio (Table 4). When MeOD was used as the quencher, a

deuterated compound (**30**) was obtained in high yield with excellent deuterium incorporation. In addition, trapping with benzoyl chloride (PhCOCl) afforded **31** in good yield. Surprisingly, reaction with methyl trifluoromethanesulfonate (MeOTf) led to methylation to give the cyclic compound **32** in 75% yield, while chlorination with carbon tetrachloride ($CCl_4$) provided cyclic compound **33** in 52% yield.

**Table 4**. Anionic monoaddition of lithium BPD with *tert*-butyl methacrylate followed by trapping with various electrophilic reagents.

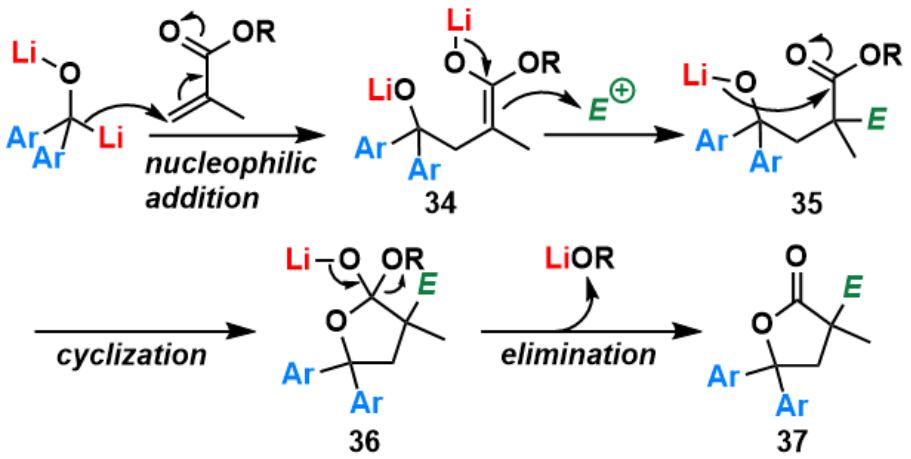



| electrophile (*E*) | product | electrophile (*E*) | product |
|---|---|---|---|
| MeO-D |  **30** 91% (>99% D) | PhCO-Cl |  **31** 72% |
| Me-OTf |  **32** 75% | Cl-$CCl_3$ |  **33** 52% |

Yields were determined by $^1$H NMR analysis using an internal standard (dimethyl terephthalate).

The plausible mechanism for these interesting cyclization processes was then examined (Scheme 3). In the anionic monoaddition of methacrylates, the living end consists of lithium enolate intermediate **34**, accompanied by a lithium alkoxide moiety. Upon introduction of an electrophile, both the lithium enolate and lithium alkoxide moieties potentially react; however, the lithium enolate moiety preferentially reacts with the electrophile to afford the ester-type intermediate **35**. Subsequent intramolecular cyclization between the lithium alkoxide moiety and the ester moiety leads to the formation of a cyclized intermediate **36**, which is subsequently converted into the ring-type monoadduct **37** through alkoxide elimination at the ester moiety.

**Scheme 3**. Plausible mechanism for the formation of chain and cyclic monoadducts.



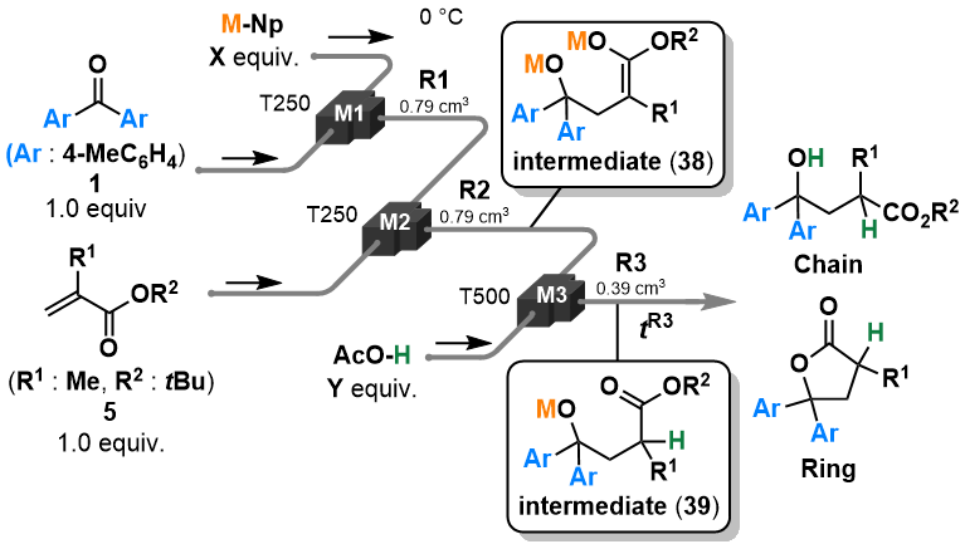

In contrast, when PhCOCl was employed as the electrophile, the linear-type monoadduct was predominantly formed. This outcome is attributed to preferential intramolecular cyclization between the ketone moiety in intermediate **35** and the alkoxide, followed by a reversible ring-opening process, ultimately leading to the formation of the linear-type monoadduct **31**. To verify this hypothesis, the cyclized intermediate was trapped via methylation, and the corresponding cyclized product was obtained in 51% yield (*see* Supporting Information for details).

To further validate this mechanistic proposal and elucidate the factors governing chain-type versus ring-type monoadduct formation, model experiments were conducted to evaluate the selectivity of electrophilic addition and the rate of intramolecular cyclization using a stoichiometric amount of HOAc (1.0 equiv.), which can react rapidly with lithium alkoxide and enolate species (Table 5). Under the previously optimized conditions, MNp was reacted with **1** to generate the corresponding BPD. Subsequent anionic monoaddition with *tert*-butyl methacrylate (**5**) afforded intermediate **38**, and upon treatment with HOAc, the intramolecular cyclization rate of intermediate **39** was examined by varying the residence time.

When 2.1 equivalents of LiNp and a residence time of 1.2 s were employed (Figure 1a), both the chain-type monoadduct **4** and the ring-type monoadduct **40** were obtained in 53% and 40% yields, respectively, upon treatment with 1.0 equivalent of HOAc (Entry 1). When more than 2.0 equivalents of HOAc were used, the formation of the chain-type monoadduct **4** became predominant, affording the product in over 93% yield (Entries 2–4). Furthermore, when 2.1 equivalents of LiNp and 1.0 equivalent of HOAc were employed (Figure 1b), only the chain-type monoadduct 4 was formed at a short residence time of 0.1 s. As the residence time increased, the formation of the ring-type monoadduct **40** gradually proceeded, and at 9.3 s, the ring-type product became predominant with a 73% yield. After the microflow reaction, additional stirring at 0 °C for 60 s further promoted cyclization, affording the ring-type monoadduct **40** in 90% yield. Under these optimized conditions using LiNp, various ring-type monoadducts were synthesized from

the previously examined benzophenone derivatives and vinyl monomers. For instance, the reaction of bis(4-methoxyphenyl)methanone (**7**) with methyl methacrylate (**14**) afforded the ring-type monoadduct **41** in 53% yield, while the reaction of benzophenone (**6**) with *tert*-butyl acrylate (**15**) gave the ring-type monoadduct **42** in 86% yield. Similarly, in reactions conducted with an excess of electrophilic reagents (MeOTf or $CCl_4$, 5.0 equiv.), the ring-type monoadducts **32** and **33** were obtained in 80% and 46% yields, respectively. In contrast, when 2.6 equivalents of KNp were used (Figure 1c), the ring-type monoadduct **40** was formed in approximately 50% yield under all residence-time conditions. These results experimentally validate the proposed mechanism. The cyclization rate of the ring-type monoadducts, formed via monoaddition intermediates and subsequent end-capping with electrophilic reagents, was found to depend on both the functional characteristics of the electrophilic reagent and the nature of the metal counterion. Therefore, the selectivity between the chain-type and ring-type monoaddition products could be controlled by modifying these conditions.

**Table 5**. Investigation of the residence time on the monoadduct structure in the flow microreactor using HOAc as an electrophile.

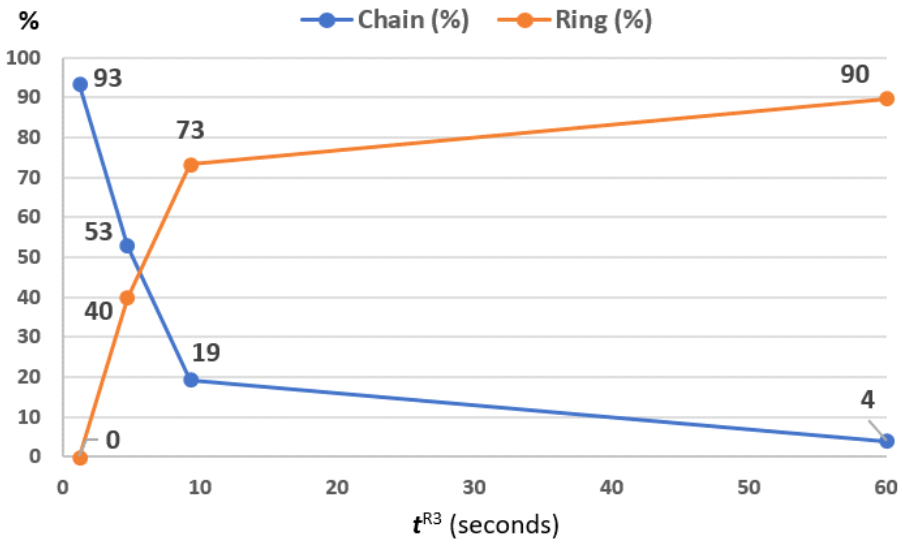


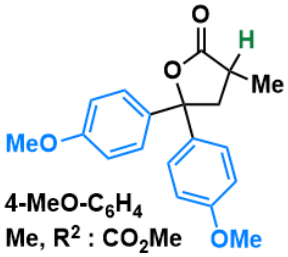
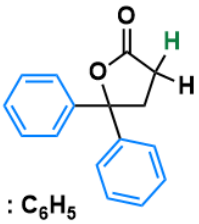

a) **Li-Np** (2.1 equiv.), $t^{R3}$: 1.2 s

| Entry | **AcO-H** (Y equiv.) | Yield (%) | |
|---|---|---|---|
| | | **Chain (4)** | **Ring (40)** |
| 1 | 0 | 73 | - |
| 2 | 1.0 | 53 | 40 |
| 3 | 2.0 | 96 | - |

| | | | |
|---|---|---|---|
| 4 | 3.0 | 93 | - |
| 5 | 5.0 | 96 | - |

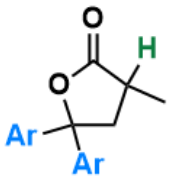
b) **Li-Np** (2.1 equiv.), **AcO-H** (1.0 equiv.)




| product | product |
|---|---|
|  Ar : 4-MeO-$C_6H_4$ <br> $R^1$ : Me, $R^2$ : $CO_2$Me <br> **41** <br> 53% |  Ar : $C_6H_5$ <br> $R^1$ : H, $R^2$ : $CO_2t$Bu <br> **42** <br> 86% |

$t^{R3}$: 5 min

c) **K-Np** (2.6 equiv.), **AcO-H** (1.0 equiv.)



**Ring (40)**

*t* : 0.08 ~ 8.77 sec.

yield : 50 ~ 52%

**Figure 1**. Results of the anionic monoaddition under microflow conditions. a) Effect of the equivalents of HOAc, b) Effect of residence time on product selectivity and substrate scope ($t^{R1}$: 4.6 s, $t^{R2}$: 3.1 s). c) Effect of the metal naphthalenide ($t^{R1}$: 4.1 s, $t^{R2}$: 2.9 s). Yields were determined by $^{1}$H NMR analysis using an internal standard (dimethyl terephthalate).

## 3-3. Conclusion

In summary, the author successfully achieved the selective generation of lithium BPD and the anionic monoaddition reactions of these species to polymerizable vinyl monomers using a fast microflow system. The results demonstrate that the flash-flow system is characterized by its ability to selectively carry out anionic monoaddition reactions with methacrylates, and subsequently, the ring-closing reaction of the alkoxide moiety with the ester moiety in methacrylates.

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## 3-5. Experimental Section

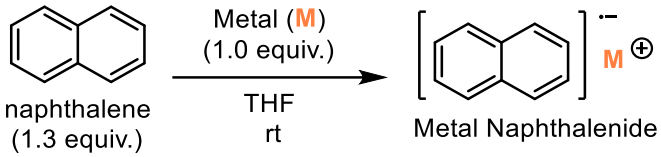
### 3-5-1. General information

$^{1}H$ and $^{13}C$ NMR spectra were recorded in on JEOL ECZ-400S spectrometer ($^{1}H$ 400 MHz, $^{13}C$ 100 MHz). Chemical shifts are recorded using TMS (0.0 ppm) signals as an internal standard for $^{1}H$ NMR, and methine signal of $CHCl_3$ for $^{13}C$ NMR (77.0 ppm) unless otherwise noted. NMR yields were calculated by $^{1}H$ NMR analyses using Dimethyl Terephthalate (cas no. 120-61-6) as an internal standard. GC analyses were performed on a SHIMADZU GC-2025 gas chromatograph equipped with a flame ionization detector using a fused silica capillary column (column, Rtx-200; 0.25 mm × 30 m). GC yields were calculated by GC analyses with *n*-tetradecane as an internal standard using calibration lines derived from commercial or isolated compounds with the internal standards. GC-MS analysis was performed on a SHIMADZU GCMS-QP2020 NX. GPC analysis was performed on a SHIMADZU CTO-20A with a Shodex RI-504 RI detector. Mass spectra were recorded on Thermo Fisher Scientific EXACTIVE plus (ESI and APCI) and JEOL JMS-700 (EI) in Instrumental Analysis Div., Global Facility Center, Creative Research Institution, Hokkaido University. Merck pre-coated silica gel $F_{254}$ plates (thickness 0.25 mm) were used for TLC analyses. Preparative GPC separation was performed on a JAI HPLC 9021 equipped with JAIGEL-1H and -2H columns. All batch reactions were carried out in a flame-dried glassware under argon atmosphere unless otherwise noted.

**Flow synthesis.** Stainless steel (SUS304) T-shaped micromixers with inner diameter of 500 μm and 250 μm were manufactured by Sanko Seiki Co., Inc. Stainless steel (SUS316) microtube reactors with 1000 μm inner diameter and PTFE tubes with inner diameter of 1000 μm were purchased from GL Sciences. The syringe pumps (Harvard PHD ULTRA) equipped with gastight syringes (SGE 50MR-LL-GT or 100MR-LL-GT) were used for introduction of the solutions into the micromixer systems *via* stainless steel fittings (GL Sciences, 1/16 OUW). Flow microreactor system is composed with stainless steel pre-cooling units (**P1**, **P2**, etc.), stainless steel microtube reactors (**R1**, **R2**, etc.), T-shaped micromixers (**M1**, **M2**, etc.), and, if necessary, PTFE tube with inner diameter of 1000 μm.

**Materials.** Dry THF and *n*-hexane were purchased from Kanto Chemical and were used after passing through the purification column in the solvent dispenser system.

### 3-5-2. Preparation of Metal Naphthalenide (MNp)




#### 3-5-2-1. LiNp, KNp

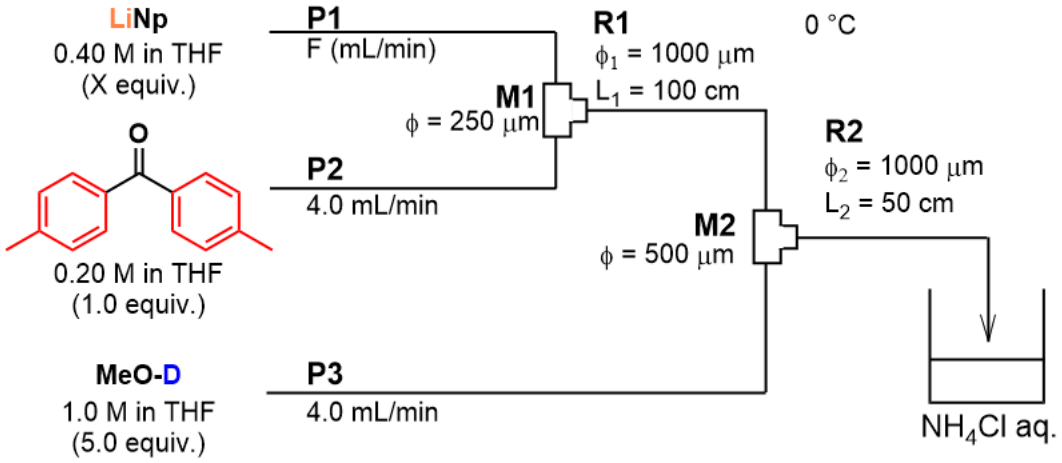
Naphthalene (2.8 g, 21.7 mmol, 1.3 equiv.) was dissolved in anhydrous THF (42.0 ml) (0.23 M). Metal (K, Li, 16.7 mmol, 1.0 equiv.) was added and the mixture was stirred for 2 h at ambient temperature until the solution became dark green.

#### 3-5-2-2. NaNp

Naphthalene (1.4 g, 11.1 mmol, 1.3 equiv.) was dissolved in anhydrous THF (97.0 ml) (114.4 μM). dispersion Na (25%wt., 0.88 mL, 198.0 mmol, 1.0 equiv.) was added and the mixture was stirred for 2 h at ambient temperature until the solution became dark green.

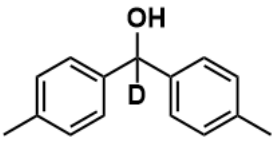
### 3-5-3. Effect of metal naphthalenides (MNp) and equivalents on selective generation of benzophenone radical anion (BPA) and dianion (BPD) in a flow microreactor.

#### 3-5-3-1. LiNp

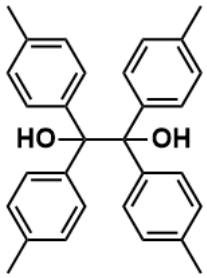



A flow microreactor system consisting of two T-shaped micromixers (**M1**, **M2**), four microtube reactors (**R1** and **R2**), and three pre-cooling units was used in a cooling bath at 0 °C (**P1** (L = 100 cm) and **P2** (100 cm) and **P3** (100 cm)). A solution of Lithium naphthalenide (0.40 M in THF, flow rate: F mL/min) and a solution of 4,4'-Dimethylbenzophenone (**1**, 0.20 M in THF, flow rate: 4.0 mL/min) were introduced to **M1** ($\phi$ = 250 μm) using syringe pumps, and the mixture was passed through **R1** ($\phi$ = 1000 μm, $L_1$ = 100 cm, residence time $t^{R1}$ = 4.7 ~ 7.9 s). The resulting solution was introduced to **M2** ($\phi$ = 500 μm), where a solution of methanol-d (1.0 M in THF) was also introduced (flow rate: 4.0 mL/min). The resulting solution was passed through **R2** ($\phi$ = 1000 μm, $L_2$ = 50 cm, residence time = 1.7 ~ 2.4 s). After a steady state was reached, the product

solution was collected for 20 seconds. To the aliquot, sat. $NH_4Cl$ aq. was added, and then the organic phase was analyzed by NMR.

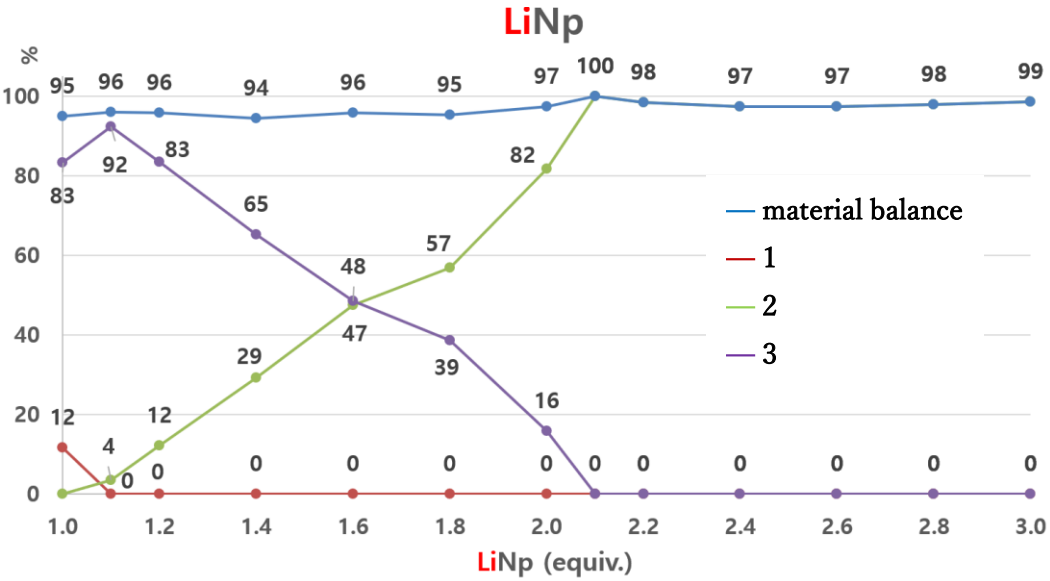



**di-p-tolylmethan-d-ol (2):** The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.26-7.24 (m, 4H), 7.13 (d, $J$ = 7.6 Hz, 4H), 2.32 (s, 6H), 2.15 (broad, 1H); $^{13}C$ NMR (100MHz, $CDCl_3$) δ 141.0 (2C), 137.1 (2C), 129.1 (4C), 126.4 (4C), 75.4, 21.1 (2C). HRMS (ESI) *m/z* Calcd for $C_{15}H_{15}ODNa$ $[M+Na]^+$ 236.1156; Found: 236.1152.




**1,1,2,2-tetra-p-tolylethane-1,2-diol (3):** The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.15 (d, $J$ = 8.0 Hz, 8H), 6.97 (d, $J$ = 8.4 Hz, 8H), 2.96 (broad, 1H), 2.28 (s, 12H); $^{13}C$ NMR (100MHz, $CDCl_3$) δ 141.4 (4C), 136.3 (4C), 128.4 (8C), 127.9 (8C), 82.8 (2C), 21.0 (4C). HRMS (ESI) *m/z* Calcd for $C_{30}H_{30}O_2Na$ $[M+Na]^+$ 445.2138; Found: 445.2130.

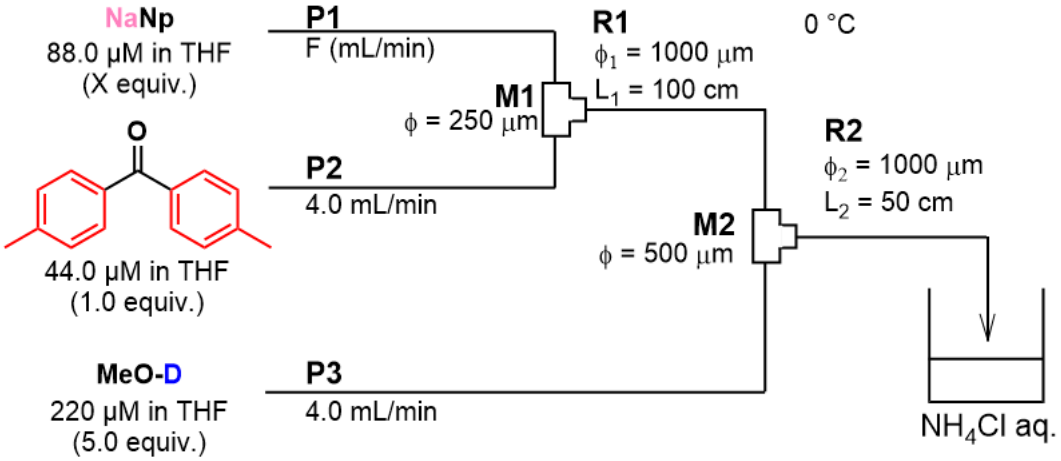
**Table 6.** investigation for the equivalent of lithium naphtalenide on synthesis of benzophenone radical anion and dianion in the flow microreactor.



| entry | F (mL/min) | equiv. (X) | $t^{R1}$ (second) | $t^{R2}$ (second) | **1** recovery (%) | yield (%) | |
|---|---|---|---|---|---|---|---|
| | | | | | | **2** | **3** |
| 1 | 2.0 | 1.0 | 7.9 | 2.4 | 12 | - | 83 |
| 2 | 2.2 | 1.1 | 7.6 | 2.3 | - | 4 (99) | 92 |
| 3 | 2.4 | 1.2 | 7.4 | 2.3 | - | 12 (96) | 83 |
| 4 | 2.8 | 1.4 | 6.9 | 2.2 | - | 29 (99) | 65 |
| 5 | 3.2 | 1.6 | 6.5 | 2.1 | - | 47 (99) | 48 |
| 6 | 3.6 | 1.8 | 6.2 | 2.0 | - | 57 (99) | 39 |
| 7 | 4.0 | 2.0 | 5.9 | 2.0 | - | 82 (98) | 16 |
| 8 | 4.2 | 2.1 | 5.7 | 1.9 | - | 100(100) | - |
| 9 | 4.4 | 2.2 | 5.6 | 1.9 | - | 98 (99) | - |
| 10 | 4.8 | 2.4 | 5.4 | 1.8 | - | 97 (99) | - |
| 11 | 5.2 | 2.6 | 5.1 | 1.8 | - | 97 (99) | - |
| 12 | 5.6 | 2.8 | 4.9 | 1.7 | - | 98 (99) | - |
| 13 | 6.0 | 3.0 | 4.7 | 1.7 | - | 99 (99) | - |

Yields were determined by $^{1}$H NMR analysis using an internal standard (dimethyl terephthalate).

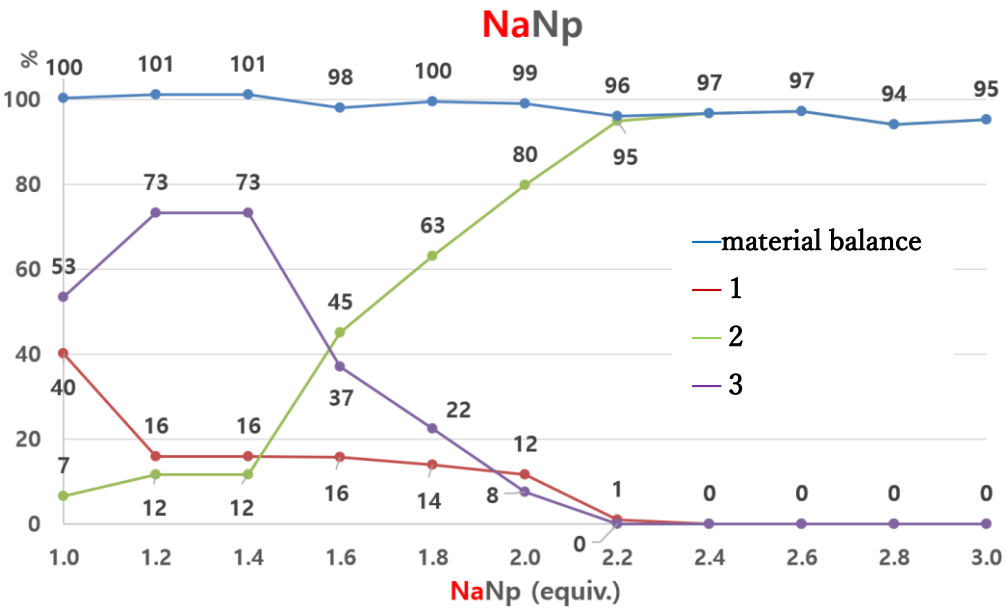
### 3-5-3-2. NaNp




A flow microreactor system consisting of two T-shaped micromixers (**M1**, **M2**), four microtube reactors (**R1** and **R2**), and three pre-cooling units was used in a cooling bath at 0 °C (**P1** (L = 100 cm) and **P2** (100 cm) and **P3** (100 cm)). A solution of sodium naphthalenide (88.0 μM in THF, flow rate: F mL/min) and a solution of 4,4'-Dimethylbenzophenone (**1**, 44.0 μM in THF, flow

rate: 4.0 mL/min) were introduced to **M1** ($\phi$ = 250 μm) using syringe pumps, and the mixture was passed through **R1** ($\phi$ = 1000 μm, $L_1$ = 100 cm, residence time $t^{R1}$ = 4.7 ~ 7.9 s). The resulting solution was introduced to **M2** ($\phi$ = 500 μm), where a solution of methanol-d (220 μM in THF) was also introduced (flow rate: 4.0 mL/min). The resulting solution was passed through **R2** ($\phi$ = 1000 μm, $L_2$ = 50 cm, residence time = 1.7 ~ 2.4 s). After a steady state was reached, the product solution was collected for 20 seconds. To the aliquot, sat. $NH_4Cl$ aq. was added, and then the organic phase was analyzed by NMR.

**Table 7.** investigation for the equivalent of sodium naphtalenide on synthesis of benzophenone radical anion and dianion in the flow microreactor.

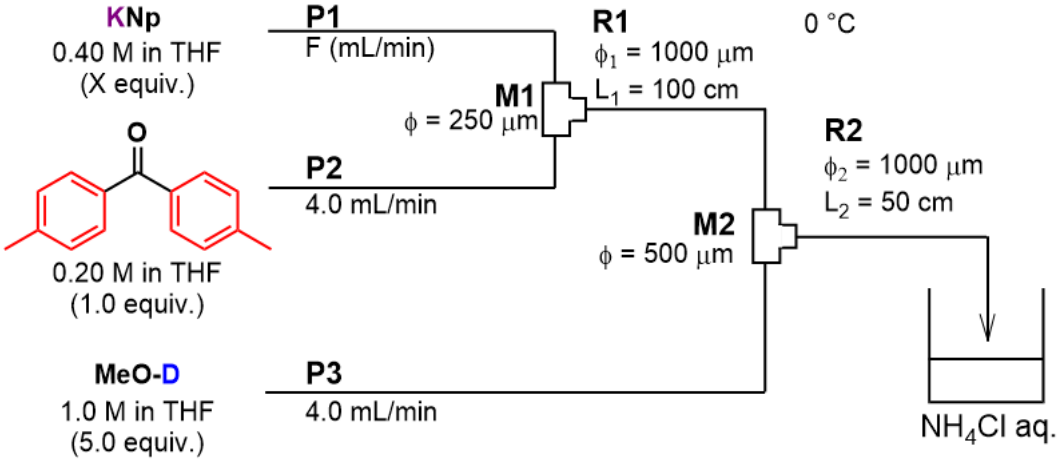



| entry | F (mL/min) | equiv. (X) | $t^{R1}$ (second) | $t^{R2}$ (second) | **1** recovery (%) | yield (%) | |
|---|---|---|---|---|---|---|---|
| | | | | | | **2** | **3** |
| 1 | 2.0 | 1.0 | 7.9 | 2.4 | 40 | 7 | 53 |
| 2 | 2.4 | 1.2 | 7.4 | 2.3 | 16 | 12 (-) | 73 |
| 3 | 2.8 | 1.4 | 6.9 | 2.2 | 16 | 12 (-) | 73 |
| 4 | 3.2 | 1.6 | 6.5 | 2.1 | 16 | 45 (91) | 37 |
| 5 | 3.6 | 1.8 | 6.2 | 2.0 | 14 | 63 (96) | 22 |
| 6 | 4.0 | 2.0 | 5.9 | 2.0 | 12 | 80 (96) | 8 |
| 7 | 4.4 | 2,2 | 5.6 | 1.9 | 1 | 95 (97) | - |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 8 | 4.8 | 2.4 | 5.4 | 1.8 | - | 97 (96) | - |
| 9 | 5.2 | 2.6 | 5.1 | 1.8 | - | 97 (97) | - |
| 10 | 5.6 | 2.8 | 4.9 | 1.7 | - | 94 (97) | - |
| 11 | 6.0 | 3.0 | 4.7 | 1.7 | - | 95 (97) | - |

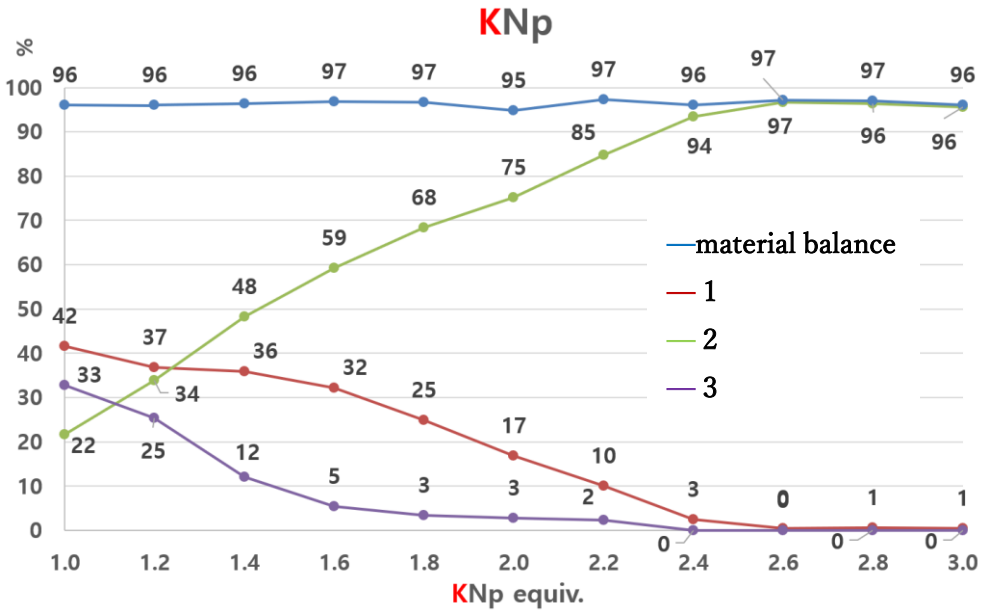
Yields were determined by $^{1}$H NMR analysis using an internal standard (dimethyl terephthalate).

### 3-5-3-3. KNp




A flow microreactor system consisting of two T-shaped micromixers (**M1**, **M2**), four microtube reactors (**R1** and **R2**), and three pre-cooling units was used in a cooling bath at 0 °C (**P1** (L = 100 cm) and **P2** (100 cm) and **P3** (100 cm)). A solution of Potassium naphthalenide (0.40 M in THF, flow rate: F mL/min) and a solution of 4,4'-Dimethylbenzophenone (0.20 M in THF, flow rate: 4.0 mL/min) were introduced to **M1** ($\phi$ = 250 μm) using syringe pumps, and the mixture was passed through **R1** ($\phi$ = 1000 μm, $L_1$ = 100 cm, residence time $t^{R1}$ = 3.9 ~ 7.9 s). The resulting solution was introduced to **M2** ($\phi$ = 500 μm), where a solution of MeOD (1.0 M in THF) was also introduced (flow rate: 4.0 mL/min). The resulting solution was passed through **R2** ($\phi$ = 1000 μm, $L_2$ = 50 cm, residence time = 1.7 ~ 2.4 s). After a steady state was reached, the product solution was collected for 20 seconds. To the aliquot, sat. $NH_4Cl$ aq. was added, and then the organic phase was analyzed by NMR.

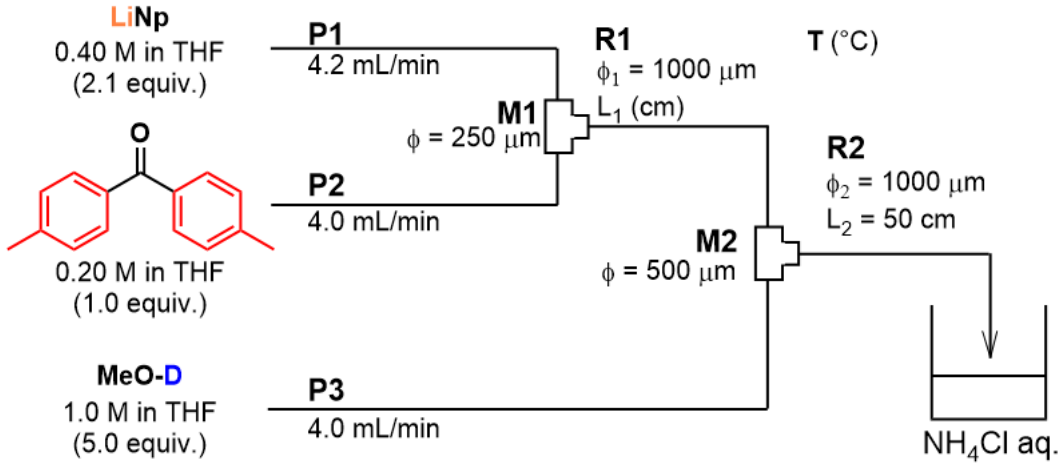
**Table 8.** investigation for the equivalent of potassium naphtalenide on synthesis of benzophenone radical anion and dianion in the flow microreactor.




| entry | F (mL/min) | equiv. (X) | $t^{R1}$ (second) | $t^{R2}$ (second) | **1** recovery (%) | yield (%) | |
|---|---|---|---|---|---|---|---|
| | | | | | | **2** | **3** |
| 1 | 2.0 | 1.0 | 7.9 | 2.4 | 42 | 22 (93) | 33 |
| 2 | 2.4 | 1.2 | 7.4 | 2.3 | 37 | 34 (94) | 25 |
| 3 | 2.8 | 1.4 | 6.9 | 2.2 | 36 | 48 (93) | 12 |
| 4 | 3.2 | 1.6 | 6.5 | 2.1 | 32 | 59 (94) | 5 |
| 5 | 3.6 | 1.8 | 6.2 | 2.0 | 25 | 68 (94) | 3 |
| 6 | 4.0 | 2.0 | 5.9 | 2.0 | 17 | 75 (94) | 3 |
| 7 | 4.4 | 2.2 | 5.6 | 1.9 | 10 | 85 (95) | 2 |
| 8 | 4.8 | 2.4 | 5.4 | 1.8 | 3 | 94 (96) | - |
| 9 | 5.2 | 2.6 | 5.1 | 1.8 | 0 | 97 (96) | - |
| 10 | 5.6 | 2.8 | 4.9 | 1.7 | 1 | 96 (96) | - |
| 11 | 6.0 | 3.0 | 4.7 | 1.7 | 1 | 96 (96) | - |

Yields were determined by $^{1}$H NMR analysis using an internal standard (dimethyl terephthalate).

### 3-5-4. Effect of temperatures and retention times on selective generation of benzophenone radical anion (BPA) and dianion (BPD) in a flow microreactor.




A flow microreactor system consisting of two T-shaped micromixers (**M1**, **M2**), four microtube reactors (**R1** and **R2**), and three pre-cooling units was used in a cooling bath at 0 °C (**P1** (L = 100 cm) and **P2** (100 cm) and **P3** (100 cm)). A solution of Lithium naphthalenide (0.40 M in THF, flow rate: 4.2 mL/min) and a solution of 4,4'-Dimethylbenzophenone (0.20 M in THF, flow rate: 4.0 mL/min) were introduced to **M1** ($\phi$ = 250 μm) using syringe pumps, and the mixture was passed through **R1** ($\phi$ = 1000 μm, $L_1$ = 3.5~400 cm, residence time $t^{R1}$ = 0.2 ~ 23.0 s). The resulting solution was introduced to **M2** ($\phi$ = 500 μm), where a solution of methanol-d (1.0 M in THF) was also introduced (flow rate: 4.0 mL/min). The resulting solution was passed through **R2** ($\phi$ = 1000 μm, $L_2$ = 50 cm, residence time = 1.9 s). After a steady state was reached, the product solution was collected for 20 seconds. To the aliquot, sat. $NH_4Cl$ aq. was added, and then the organic phase was analyzed by NMR.

**Table 9.** investigation for the temperature and residence time on synthesis of benzophenone dianion in the flow microreactor.

| entry | T (°C) | $t^{R1}$ (second) | **1** recovery (%) | yield (%) **2** | **3** |
|---|---|---|---|---|---|
| 1 | 20 | 0.20 | 100 | 91 (99) | - |
| 2 | | 0.29 | 100 | 92 (99) | - |
| 3 | | 0.72 | 100 | 94 (>99) | - |
| 4 | | 1.44 | 100 | 94 (99) | 2 |
| 5 | | 2.87 | 100 | 99 (99) | 2 |
| 6 | | 5.75 | 100 | 98 (99) | 2 |

| | | | | | |
|---|---|---|---|---|---|
| 7 | | 11.5 | 100 | 96 (99) | - |
| 8 | | 23.0 | 100 | 94 (99) | - |
| 9 | 0 | 0.20 | 100 | 92 (>99) | - |
| 10 | | 0.29 | 100 | 91 (>99) | - |
| 11 | | 0.72 | 100 | 92 (>99) | - |
| 12 | | 1.44 | 100 | 95 (>99) | - |
| 13 | | 2.87 | 100 | 93 (>99) | - |
| 14 | | 5.75 | 100 | 95 (>99) | - |
| 15 | | 11.5 | 100 | 93 (>99) | - |
| 16 | | 23.0 | 100 | 92 (>99) | - |
| 17 | –20 | 0.20 | 100 | 90 (98) | - |
| 18 | | 0.29 | 100 | 91 (>99) | - |
| 19 | | 0.72 | 100 | 91 (>99) | - |
| 20 | | 1.44 | 100 | 93 (>99) | - |
| 21 | | 2.87 | 100 | 93 (98) | - |
| 22 | | 5.75 | 100 | 95 (99) | - |
| 23 | | 11.5 | 100 | 96 (99) | - |
| 24 | | 23.0 | 100 | 91 (>99) | - |
| 25 | –40 | 0.20 | 100 | 74 (>99) | 10 |
| 26 | | 0.29 | 100 | 78 (99) | 5 |
| 27 | | 0.72 | 100 | 81 (>99) | 3 |
| 28 | | 1.44 | 100 | 86 (>99) | 2 |
| 29 | | 2.87 | 100 | 86 (>99) | 1 |
| 30 | | 5.75 | 100 | 95 (99) | - |
| 31 | | 11.5 | 100 | 96 (>99) | - |
| 32 | | 23.0 | 100 | 89 (>99) | - |
| 33 | –60 | 0.20 | 85 | 37 (>99) | 18 |
| 34 | | 0.29 | 96 | 37 (>99) | 22 |
| 35 | | 0.72 | 94 | 49 (>99) | 19 |
| 36 | | 1.44 | 99 | 58 (>99) | 14 |
| 37 | | 2.87 | 100 | 62 (>99) | 13 |

| | | | | | |
|---|---|---|---|---|---|
| 38 | | 5.75 | 100 | 74 (>99) | 10 |
| 39 | | 11.5 | 100 | 68 (>99) | 12 |
| 40 | | 23.0 | 100 | 81 (>99) | 5 |
| 41 | –78 | 0.20 | 62 | 33 (>99) | 12 |
| 42 | | 0.29 | 57 | 29 (>99) | 12 |
| 43 | | 0.72 | 93 | 40 (>99) | 24 |
| 44 | | 1.44 | 86 | 35 (>99) | 26 |
| 45 | | 2.87 | 90 | 43 (>99) | 21 |
| 46 | | 5.75 | 88 | 31 (>99) | 27 |
| 47 | | 11.5 | 97 | 47 (>99) | 23 |
| 48 | | 23.0 | 94 | 55 (>99) | 17 |

Yields were determined by $^{1}$H NMR analysis using an internal standard (dimethyl terephthalate).

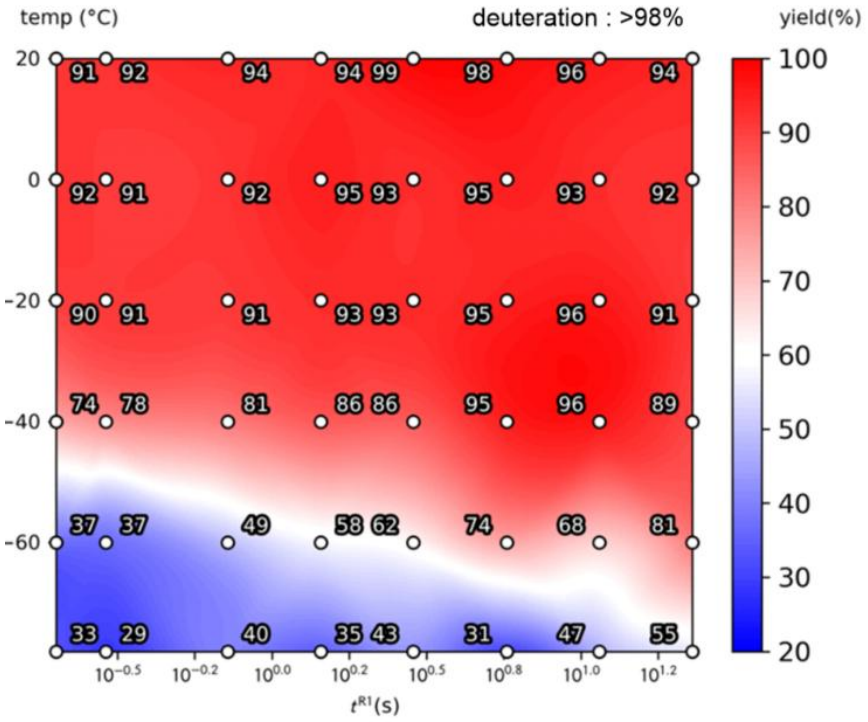
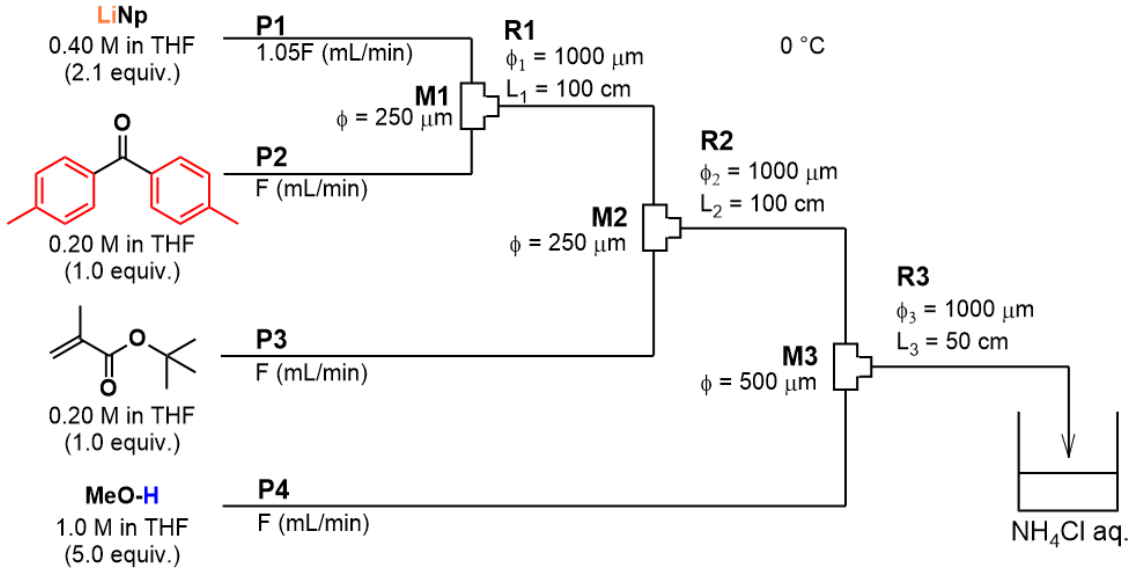



**Figure 2.** Temperature-residence time contour mapping for the generation of benzophenone dianion in the flow microreactor. Horizontal axis: residence time $t^{R1}$ (s), vertical axis: temperature (°C), the designated number on the circle dot: yield of **2**.

### 3-5-5. Effect of Flow Rate on the Monoaddition of BPD in a Flow Microreactor

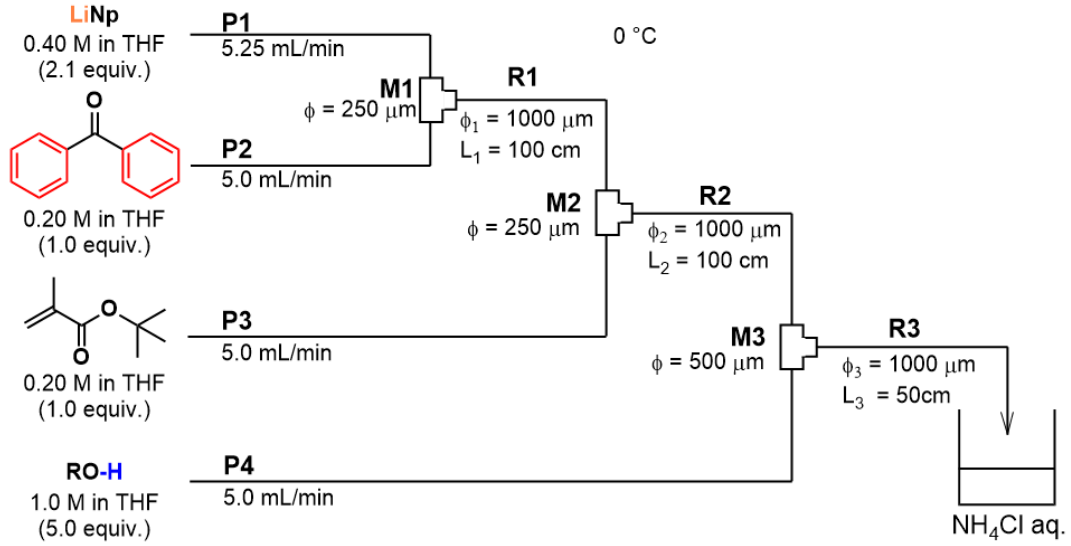



A flow microreactor system consisting of three T-shaped micromixers (**M1**, **M2** and **M3**), three microtube reactors (**R1**, **R2** and **R3**), and four pre-cooling units was used in a cooling bath at 0 °C (**P1** (L = 100 cm) and **P2** (100 cm) and **P3** (100 cm) and **P4** (100 cm)). A solution of lithium naphthalenide (0.42 M in THF, flow rate: F (mL/min), 2.1 equiv.) and a solution of benzophenone (0.20 M in THF, flow rate: F (mL/min), 1.0 equiv.) were introduced into **M1** (ϕ = 250 μm) using syringe pumps, and the mixture was passed through **R1** (ϕ = 1000 μm, $L_1$ = 100 cm, residence time $t^{R1}$). The resulting solution was introduced into **M2** (ϕ = 250 μm), where a solution of *tert*-Butyl methacrylate (0.20 M in THF) was also introduced (flow rate: F (mL/min)). The resulting solution was passed through **R2** (ϕ = 1000 μm, $L_2$ = 100 cm, residence time $t^{R2}$). The resulting solution was introduced into **M3** (ϕ = 500 μm), where a solution of MeOH (1.0 M in THF) was also introduced (flow rate: F mL/min, 5.0 equiv.). The resulting solution was passed through **R3** (ϕ = 1000 μm, $L_3$ = 50 cm, residence time $t^{R3}$). After a steady state was reached, the product solution was collected for 30 s. To the aliquot, sat. $NH_4Cl$ aq. was added, and then the organic phase was analyzed by NMR.

| entry | F (mL/min) | $t^{R1}$ (second) | $t^{R2}$ (second) | $t^{R3}$ (second) | yield (%) | |
|---|---|---|---|---|---|---|
| | | | | | Chain | Ring |
| 1 | 2 | 11.8 | 7.9 | 2.9 | 65 | 9 |
| 2 | 3 | 7.9 | 5.2 | 2.0 | 80 | 2 |
| 3 | 4 | 5.9 | 3.9 | 1.5 | 82 | - |
| 4 | 5 | 4.7 | 3.1 | 1.2 | 96 | - |

Yields were determined by $^{1}$H NMR analysis using an internal standard (dimethyl terephthalate).

### 3-5-6. Effect of RO-H on monoaddition of BPD in a flow microreactor.

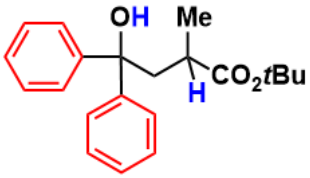



A flow microreactor system consisting of three T-shaped micromixers (**M1**, **M2** and **M3**), three microtube reactors (**R1**, **R2** and **R3**), and four pre-cooling units was used in a cooling bath at 0 °C (**P1** (L = 100 cm) and **P2** (100 cm) and **P3** (100 cm) and **P4** (100 cm)). A solution of lithium naphthalenide (0.40 M in THF, flow rate: 5.25 mL/min) and a solution of benzophenone (0.20 M in THF, flow rate: 5.0 mL/min) were introduced to **M1** ($\phi$ = 250 μm) using syringe pumps, and the mixture was passed through **R1** ($\phi$ = 1000 μm, $L_1$ = 100 cm, residence time $t^{R1}$ = 4.6 s). The resulting solution was introduced to **M2** ($\phi$ = 250 μm), where a solution of *t*-Butyl methacrylate (0.20 M in THF) was also introduced (flow rate: 5.0 mL/min). The resulting solution was passed through **R2** ($\phi$ = 1000 μm, $L_2$ = 100 cm, residence time = 3.1 s). The resulting solution was introduced to **M3** ($\phi$ = 500 μm), where a solution of RO-H (1.0 M in THF) was also introduced (flow rate: 5.0 mL/min, 5.0 equiv.). The resulting solution was passed through **R3** ($\phi$ = 1000 μm, $L_3$ = 50 cm, residence time = 1.2 s). After a steady state was reached, the product solution was collected for 30 seconds. To the aliquot, sat. $NH_4Cl$ aq. was added, and then the organic phase was analyzed by NMR.

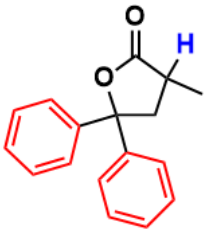
**Table 10.** investigation for the quenching reagent on anionic monoaddition of benzophenone dianion with *t*-BuMA.

| entry | RO-H | yield (%) | |
|---|---|---|---|
| | | Chain | Ring |
| 1 | MeO-H | 36 | 57 |
| 2 | AcO-H | 89 | - |
| 3 | BzO-H | 96 | - |

Yields were determined by $^{1}$H NMR analysis using an internal standard (dimethyl terephthalate).

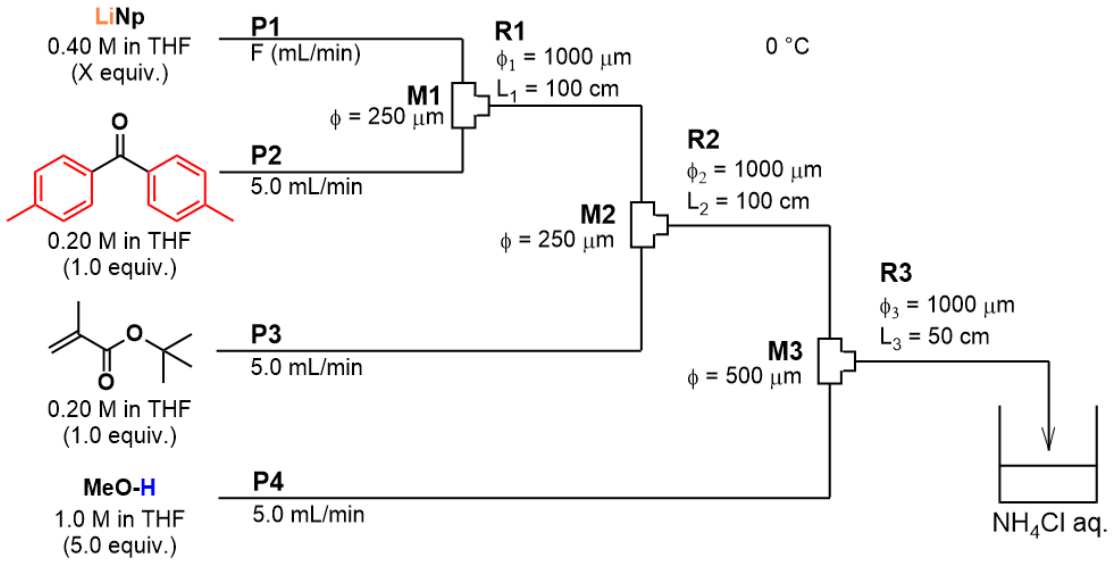



***tert*-butyl 4-hydroxy-2-methyl-4,4-diphenylbutanoate (17) :** The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$). $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.42 (t, *J* = 6.8 Hz, 4H), 7.28 (q, *J* = 8.8 Hz, 4H), 7.22-7.16 (m, 2H), 3.22 (s, 1H), 2.76 (q, *J* = 5.2 Hz, 1H), 2.38-2.30 (m, 2H), 1.42 (s, 9H), 1.10 (t, *J* = 7.6 Hz, 3H); $^{13}$C NMR (100MHz, $CDCl_3$) δ 177.6, 148.1, 145.9, 128.1 (2C), 128.0 (2C), 126.8, 126.5, 126.0 (2C), 125.9 (2C), 80.5, 77.6, 45.1, 36.4, 27.9 (3C), 19.5. HRMS (ESI) *m/z* Calcd for $C_{21}H_{26}O_3Na$ $[M+Na]^+$ 349.1774; Found: 349.1172

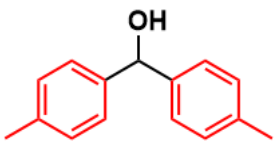



**3-methyl-5,5-diphenyldihydrofuran-2(3H)-one (1S) :** The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$). The spectral data were identical to those of reported in the literature.[1)]

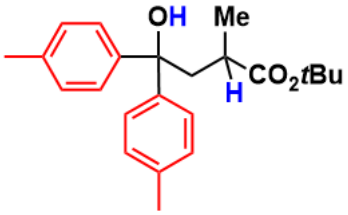
### 3-5-7. Effect of equivalents of LiNp on monoaddition of BPD in a flow microreactor.




A flow microreactor system consisting of three T-shaped micromixers (**M1**, **M2** and **M3**), three microtube reactors (**R1**, **R2** and **R3**), and four pre-cooling units was used in a cooling bath at 0 °C (**P1** (L = 100 cm) and **P2** (100 cm) and **P3** (100 cm) and **P4** (100 cm)). A solution of lithium naphthalenide (0.40 M in THF, flow rate: F mL/min) and a solution of benzophenone (0.20 M in THF, flow rate: 5.0 mL/min) were introduced to **M1** (ϕ = 250 μm) using syringe pumps, and the mixture was passed through **R1** (ϕ = 1000 μm, $L_1$ = 100 cm, residence time $t^{R1}$). The resulting solution was introduced to **M2** (ϕ = 250 μm), where a solution of *tert*-Butyl methacrylate (0.20 M in THF) was also introduced (flow rate: 5.0 mL/min). The resulting solution was passed through **R2** (ϕ = 1000 μm, $L_2$ = 100 cm, residence time $t^{R2}$). The resulting solution was introduced to **M3** (ϕ = 500 μm), where a solution of MeOH (1.0 M in THF) was also introduced (flow rate: 5.0 mL/min, 5.0 equiv.). The resulting solution was passed through **R3** (ϕ = 1000 μm, $L_3$ = 50 cm, residence time $t^{R3}$). After a steady state was reached, the product solution was collected for 30 s. To the aliquot, sat. $NH_4Cl$ aq. was added, and then the organic phase was analyzed by NMR.




**di-p-tolylmethanol (2S) :** The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$). The spectral data were identical to those of reported in the literature.[2)]



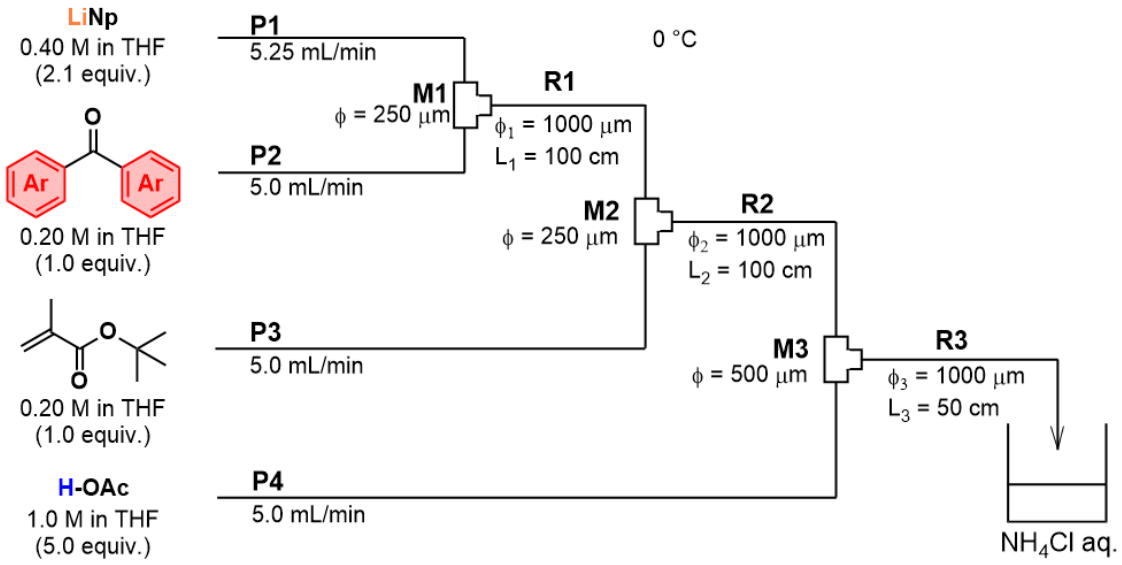

***tert*-butyl 4-hydroxy-2-methyl-4,4-di-p-tolylbutanoate (4) :** The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.29 (t, *J* = 7.6 Hz, 4H), 7.09 (t, *J* = 8.8 Hz, 4H), 3.02 (s, 1H), 2.73 (dd, *J* = 14.0, 9.6 Hz, 1H), 2.38-2.26 (m, 8H), 1.42 (s, 9H), 1.10 (t, *J* = 7.6 Hz, 3H); $^{13}$C NMR (100MHz, $CDCl_3$) δ 177.5, 145.4, 143.2, 136.3, 135.9, 128.7 (4C), 125.9 (2C), 125.8 (2C), 80.3, 77.5, 45.2, 36.4, 27.9 (3C), 20.9 (2C), 19.5. HRMS (ESI) *m/z* Calcd for $C_{23}H_{30}O_3Na$ $[M+Na]^+$ 377.2087; Found: 377.2078.

**Table 11.** investigation for the equivalent of lithium naphtalenide on anionic monoaddition of benzophenone dianion with *t*-BuMA.

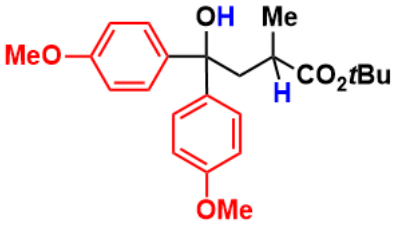
| entry | F (mL/min) | equiv. (X) | $t^{R1}$ (second) | $t^{R2}$ (second) | $t^{R3}$ (second) | **1** conversion (%) | yield (%) | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | **4** | **3** | **2S** |
| 1 | 2.75 | 1.1 | 6.1 | 3.7 | 1.3 | 96 | 5 | 84 | - |
| 2 | 3.75 | 1.5 | 5.4 | 3.4 | 1.3 | 97 | 39 | 50 | - |
| 3 | 5.25 | 2.1 | 4.6 | 3.1 | 1.2 | 100 | 96 | - | - |
| 4 | 7.50 | 3.0 | 3.8 | 2.7 | 1.0 | 100 | 41 | - | 47 |

Yields were determined by $^1$H NMR analysis using an internal standard (dimethyl terephthalate).

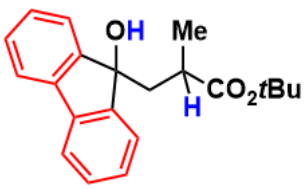
### 3-5-8. Synthesis of monoaddition product via litihium benzophenone's derivative dianions in a flow microreactor.



A flow microreactor system consisting of three T-shaped micromixers (**M1**, **M2** and **M3**), three microtube reactors (**R1**, **R2** and **R3**), and four pre-cooling units was used in a cooling bath at 0 °C (**P1** (L = 100 cm) and **P2** (100 cm) and **P3** (100 cm) and **P4** (50 cm)). A solution of lithium naphthalenide (0.40 M in THF, flow rate: 5.25 mL/min) and a solution of benzophenone's derivative (0.20 M in THF, flow rate: 5.0 mL/min) were introduced to **M1** ($\phi$ = 250 µm) using syringe pumps, and the mixture was passed through **R1** ($\phi$ = 1000 µm, $L_1$ =100 cm, residence time $t^{R1}$ = 4.6 s). The resulting solution was introduced to **M2** ($\phi$ = 250 µm), where a solution of *tert*-butyl methacrylate (0.20 M in THF) was also introduced (flow rate: 5.0 mL/min). The resulting solution was passed through **R2** ($\phi$ = 1000 µm, $L_2$ = 100 cm, residence time = 3.1 s). The resulting solution was introduced to **M3** ($\phi$ = 500 µm), where a solution of acetic acid (1.0 M in THF) was also introduced (flow rate: 5.0 mL/min). The resulting solution was passed through **R3** ($\phi$ = 1000 µm, $L_3$ = 50 cm, residence time = 1.2 s). After a steady state was reached, the product solution was collected for 30 seconds. To the aliquot, sat. $NH_4Cl$ aq. was added, and then the organic phase was analyzed by NMR.

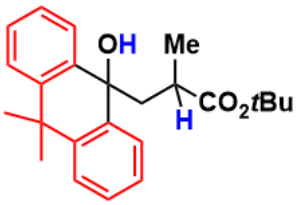



***tert*-butyl 4-hydroxy-4,4-bis(4-methoxyphenyl)-2-methylbutanoate (18) :** Obtained from bis(4-methoxyphenyl)methanone (**7**) as the benzophenone's derivative in 89% yield (NMR yield). Yields were determined by NMR analysis using an internal standard (dimethyl terephthalate). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 71% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.31 (t, *J* = 7.2 Hz, 4H), 6.82 (dd, *J* = 11.6, 8.4 Hz, 4H), 3.77 (d, *J* = 8.4 Hz, 6H), 3.03 (broad, 1H), 2.73 (ddd, *J* = 14.0, 9.6, 1.2 Hz, 1H), 2.38-2.30 (m, 1H), 2.24 (dd, *J* = 14.4, 2.0 Hz, 1H), 1.43 (s, 9H), 1.11 (d, *J* = 7.6 Hz, 3H); $^{13}$C NMR (100MHz, $CDCl_3$) δ 177.6, 158.3, 158.0, 140.7, 138.4, 127.2 (2C), 127.1 (2C), 113.3 (2C), 113.2 (2C), 80.4, 77.2, 55.1 (2C), 45.4, 36.4, 27.9 (3C), 19.5. HRMS (ESI) *m/z* Calcd for $C_{23}H_{30}O_5Na$ $[M+Na]^+$ 409.1986; Found: 409.1981.

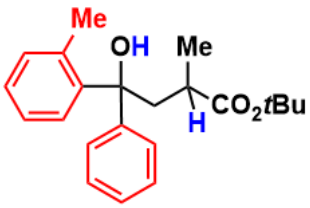



***tert*-butyl 3-(9-hydroxy-9H-fluoren-9-yl)-2-methylpropanoate (19) :** Obtained from 9H-fluoren-9-one (**8**) as the benzophenone's derivative in 88% yield (NMR yield). Yields were determined by NMR analysis using an internal standard (dimethyl terephthalate). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 74% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.58-7.53 (m, 3H), 7.48-7.46 (m, 1H), 7.34-7.23 (m, 4H), 2.76-2.70 (m, 1H), 2.57 (broad,

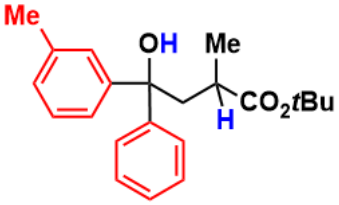
1H), 2.09-2.06 (m, 1H), 1.90-1.85 (m, 1H), 1.29 (s, 9H), 0.89-0.86 (m, 3H); $^{13}$C NMR (100MHz, $CDCl_3$) δ 176.1, 148.9, 147.6, 139.5, 139.3, 128.9 (2C), 127.8 (2C), 124.7, 123.4, 119.9, 119.8, 81.8, 79.8, 42.5, 36.7, 27.8 (3C), 19.4. HRMS (ESI) *m/z* Calcd for $C_{21}H_{24}O_3Na$ $[M+Na]^+$ 347.1618; Found: 347.1612.




***tert*-butyl 3-(9-hydroxy-10,10-dimethyl-9,10-dihydroanthracen-9-yl)-2-methylpropanoate (20) :** Obtained from 10,10-dimethylanthracen-9(10H)-one (**9**) as the benzophenone's derivative in 81% yield (NMR yield). Yields were determined by NMR analysis using an internal standard (dimethyl terephthalate). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 69% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.81-7.78 (m, 2H), 7.52 (d, $J$ = 7.2 Hz, 2H), 7.34-7.26 (m, 4H), 2.98 (broad, 1H), 2.56 (dd, $J$ = 8.8, 14.0 Hz, 1H), 2.16-2.08 (m, 1H), 1.77-1.68 (m, 4H), 1.62 (s, 3H), 1.28 (s, 9H), 0.82 (d, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (100MHz, $CDCl_3$) δ 176.2, 142.6, 142.5, 139.9, 138.4, 127.6 (2C), 126.9, 126.5, 126.1 (2C), 125.9 (2C), 79.8, 72.1, 50.9, 37.5, 36.5, 34.9, 32.6, 27.8 (3C), 19.6. HRMS (ESI) *m/z* Calcd for $C_{24}H_{30}O_3Na$ $[M+Na]^+$ 389.2087; Found: 389.2081.



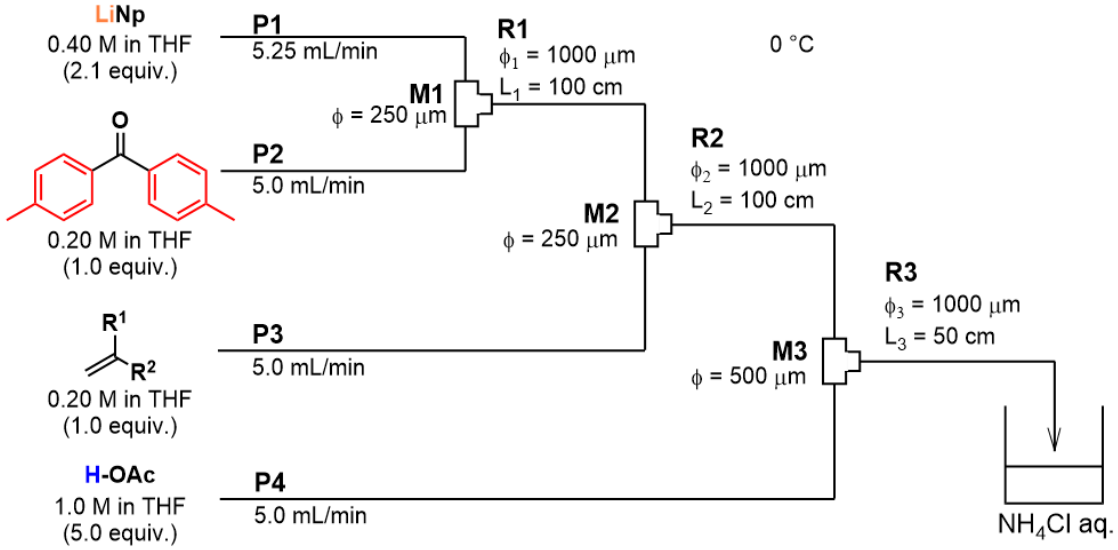

***tert*-butyl 4-hydroxy-2-methyl-4-phenyl-4-(o-tolyl)butanoate (21) :** Obtained from phenyl(o-tolyl)methanone (**10**) as the benzophenone's derivative in 59% yield (NMR yield). Yields were determined by NMR analysis using an internal standard (dimethyl terephthalate). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 44% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.73-7.66 (m, 1H), 7.31-7.16 (m, 7H), 7.08-7.05 (m, 1H), 3.34 (broad, 1H), 2.95-2.75 (m, 1H), 2.43-2.15 (m, 2H)
, 1.44-1.41 (m, 9H), 1.16-1.03 (m, 3H); $^{13}$C NMR (100MHz, $CDCl_3$) δ 177.6, 147.3-145.6, 144.8-143.0, 138.1-136.3, 132.6-132.4, 128.1-125.0 (8C), 80.5-80.2, 78.3-77.9, 46.1-44.0, 36.9-35.8, 28.0-27.9 (3C), 21.5-21.3, 19.6. HRMS (ESI) *m/z* Calcd for $C_{22}H_{28}O_3Na$ $[M+Na]^+$ 363.1931; Found: 363.1925.



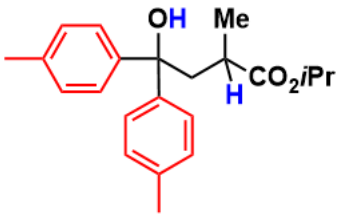

***tert*-butyl 4-hydroxy-2-methyl-4-phenyl-4-(m-tolyl)butanoate (22) :** Obtained from phenyl(m-tolyl)methanone (**11**) as the benzophenone's derivative in 84% yield (NMR yield). Yields were determined by NMR analysis using an internal standard (dimethyl terephthalate). The reaction mixture was purified by

Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 74% isolated yield. $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.42 (t, $J$ = 6.8 Hz, 2H), 7.30 (dd, $J$ = 8.4, 7.6 Hz, 3H), 7.23-7.15 (m, 3H), 7.03 (m, 1H), 3.15 (broad, 1H), 2.77-2.71 (m, 1H), 2.39-2.31 (m, 5H), 1.43 (s, 9H), 1.11 (dd, $J$ = 6.8, 4.8 Hz, 3H); $^{13}C$ NMR (100MHz, $CDCl_3$) δ 177.8, 148.4-148.3, 146.1-146.0, 137.8-137.7, 128.2-126.0 (8C), 123.3-123.1, 80.6, 77.8, 45.3, 36.6, 28.1 (3C), 21.8-21.7, 19.6. HRMS (ESI) *m/z* Calcd for $C_{22}H_{28}O_3Na$ $[M+Na]^+$ 363.1931; Found: 363.1926.

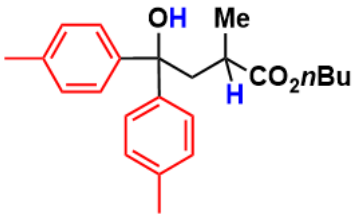
### 3-5-9. Synthesis of monoaddition product via vinyl monomers in a flow microreactor.



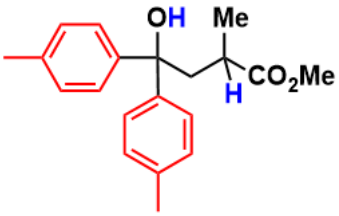

A flow microreactor system consisting of three T-shaped micromixers (**M1**, **M2** and **M3**), three microtube reactors (**R1**, **R2** and **R3**), and four pre-cooling units was used in a cooling bath at 0 °C (**P1** (L = 100 cm) and **P2** (100 cm) and **P3** (100 cm) and **P4** (50 cm)). A solution of lithium naphthalenide (0.40 M in THF, flow rate: 5.25 mL/min) and a solution of 4,4'-Dimethylbenzophenone (0.20 M in THF, flow rate: 5.0 mL/min) were introduced to **M1** ($\phi$ = 250 μm) using syringe pumps, and the mixture was passed through **R1** ($\phi$ = 1000 μm, 100 cm, residence time $t^{R1}$ = 4.6 s). The resulting solution was introduced to **M2** ($\phi$ = 250 μm), where a solution of vinyl monomer (0.20 M in THF) was also introduced (flow rate: 5.0 mL/min). The resulting solution was passed through **R2** ($\phi$ = 1000 μm, $L_2$ (cm), residence time (s)). The resulting solution was introduced to **M3** ($\phi$ = 500 μm), where a solution of acetic acid (1.0 M in THF) was also introduced (flow rate: 5.0 mL/min). The resulting solution was passed through **R3** ($\phi$ = 1000 μm, 50 cm, residence time = 1.2 s). After a steady state was reached, the product solution was collected for 30 seconds. To the aliquot, sat. $NH_4Cl$ aq. was added, and then the organic phase was analyzed by NMR.



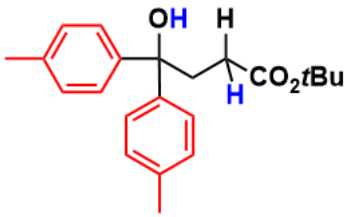

**isopropyl 4-hydroxy-2-methyl-4,4-di-p-tolylbutanoate (23) :** Obtained from *iso*-propyl methacrylate (**12**) as the vinyl monomer and 100 cm (3.1 s) as $L_2$ in 83% yield (NMR yield). Yields were determined by NMR analysis using an internal standard (dimethyl terephthalate). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 64% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.28 (t, $J$ = 8.4 Hz, 4H), 7.09 (t, $J$ = 8.4 Hz, 4H), 4.93 (septet, $J$ = 6.4 Hz, 1H), 2.85-2.76 (m, 2H), 2.46-2.37 (m, 1H), 2.32-2.29 (m, 7H), 1.20 (t, $J$ = 6.0 Hz, 6H), 1.12 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (100MHz, $CDCl_3$) δ 177.6, 145.2, 143.1, 136.4, 136.0, 128.7 (4C), 125.8 (4C), 77.5, 67.7, 45.2, 35.7, 21.7, 21.6, 20.9 (2C), 19.4. HRMS (ESI) *m/z* Calcd for $C_{22}H_{28}O_3Na$ $[M+Na]^+$ 363.1931; Found: 363.1925.



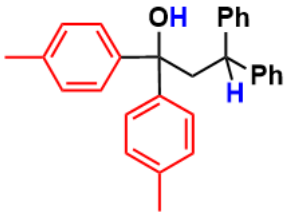

**butyl 4-hydroxy-2-methyl-4,4-di-p-tolylbutanoate (24) :** Obtained from *normal*-butyl methacrylate (**13**) as the vinyl monomer and 100 cm (3.1 s) as $L_2$ in 68% yield (NMR yield). Yields were determined by NMR analysis using an internal standard (dimethyl terephthalate). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 53% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.32 (dd, $J$ = 6.8, 8.0 Hz, 4H), 7.12 (t, $J$ = 8.0 Hz, 4H), 4.00 (t, $J$ = 6.0 Hz, 2H), 2.87-2.82 (m, 2H), 2.55-2.47 (m, 1H), 2.37-2.32 (m, 7H), 1.63-1.56 (m, 2H), 1.39 (sextet, $J$ = 7.6 Hz, 2H), 1.16 (d, $J$ = 7.2 Hz, 3H), 0.96 (t, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (100MHz, $CDCl_3$) δ 178.1, 145.0, 143.2, 136.3, 136.0, 128.7 (4C), 125.8 (4C), 77.2, 64.4, 45.3, 35.5, 30.4, 20.9 (2C), 19.4, 19.0, 13.7. HRMS (ESI) *m/z* Calcd for $C_{23}H_{30}O_3Na$ $[M+Na]^+$ 377.2087; Found: 377.2084.




**methyl 4-hydroxy-2-methyl-4,4-di-p-tolylbutanoate (25) :** Obtained from methyl methacrylate (**14**) as the vinyl monomer and 100 cm (3.1 s) as $L_2$ in 56% yield (NMR yield). Yields were determined by NMR analysis using an internal standard (dimethyl terephthalate). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 41% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.28 (t, $J$ = 8.4 Hz, 4H), 7.09 (t, $J$ = 8.0 Hz, 4H), 3.57 (s, 3H), 2.82 (dd, $J$ = 14.0, 9.6 Hz, 1H), 2.65 (broad, 1H), 2.54-2.48 (m, 1H), 2.33-2.29 (m, 7H), 1.13 (d, $J$ = 7.2 Hz, 3H); $^{13}$C NMR (100MHz, $CDCl_3$) δ 178.6, 145.0, 143.3, 136.6, 136.3, 128.9 (4C), 125.9 (4C), 77.5, 51.9, 45.6, 35.5, 21.1 (2C), 19.5. HRMS (ESI) *m/z* Calcd for $C_{20}H_{24}O_3Na$ $[M+Na]^+$ 335.1618; Found: 335.1612.

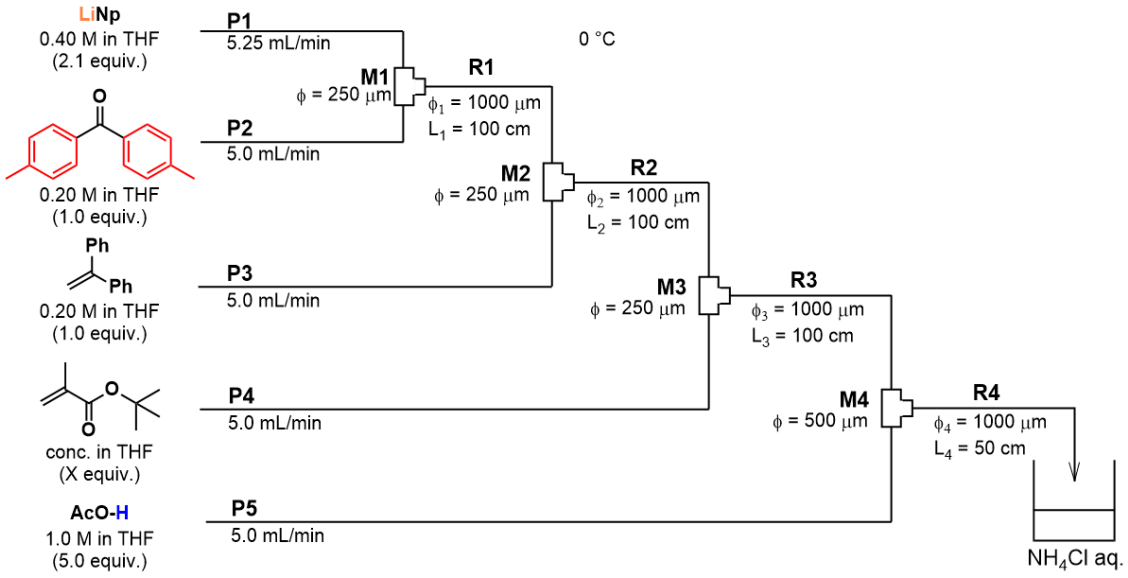



**tert-butyl 4-hydroxy-4,4-di-p-tolylbutanoate (26) :** Obtained from *tert*-butyl acrylate (**15**) as the vinyl monomer and 100 cm (3.1 s) as $L_2$ in 81% yield (NMR yield). Yields were determined by NMR analysis using an internal standard (dimethyl terephthalate). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 69% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.34 (d, $J$ = 8.0 Hz, 4H), 7.14 (d, $J$ = 8.4 Hz, 4H), 2.94 (broad, 1H), 2.59 (t, $J$ = 7.2 Hz, 2H), 2.34-2.28 (m, 8H), 1.45 (s, 9H); $^{13}$C NMR (100MHz, $CDCl_3$) δ 174.0, 143.9 (2C), 136.2 (2C), 128.7 (4C), 125.8 (4C), 80.3, 77.1, 36.3, 30.3, 27.9 (3C), 20.9 (2C). HRMS (ESI) *m/z* Calcd for $C_{22}H_{28}O_3Na$ $[M+Na]^+$ 363.1931; Found: 363.1924.

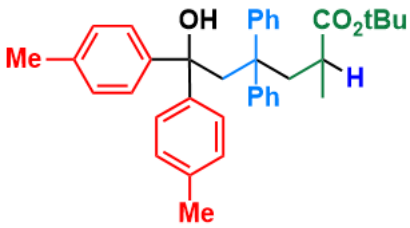



**3,3-diphenyl-1,1-di-p-tolylpropan-1-ol (27) :** Obtained from diphenyl ethylene (**16**) as the vinyl monomer and 800 cm (24.7 s) as $L_2$ in 75% yield and diphenyl ethylene was recovered in 17% yield (NMR yield). Yields were determined by NMR analysis using an internal standard (dimethyl terephthalate). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 67% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.30-7.23 (m, 8H), 7.20-7.09 (m, 10H), 4.03 (t, $J$ = 7.2 Hz, 1H), 3.15 (d, $J$ = 6.4 Hz, 2H), 2.31 (s, 6H), 1.85 (broad, 1H); $^{13}$C NMR (100MHz, $CDCl_3$) δ 145.2, 144.1, 136.2 (2C), 128.8 (4C), 128.7 (5C), 128.4, 127.8 (4C), 126.3 (2C), 125.8 (4C), 78.8, 47.4, 47.3, 20.9 (2C). HRMS (ESI) *m/z* Calcd for $C_{29}H_{28}ONa$ $[M+Na]^+$ 415.2032; Found: 415.2026.

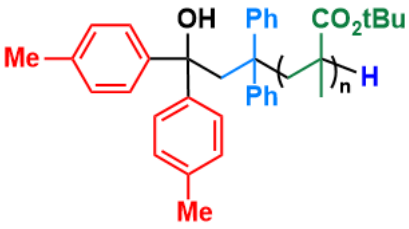
**Synthesis of sequence oligomer in a flow microreactor.**



A flow microreactor system consisting of four T-shaped micromixers (**M1**, **M2, M3** and **M4**), four microtube reactors (**R1**, **R2, R3** and **R4**), and five pre-cooling units was used in a cooling bath at 0 °C (**P1** (L = 100 cm) and **P2** (100 cm) and **P3** (100 cm) and **P4** (100 cm) and **P5** (100 cm)). A solution of lithium naphthalenide (0.40 M in THF, flow rate: 5.25 mL/min) and a solution of 4,4'-Dimethylbenzophenone (0.20 M in THF, flow rate: 5.0 mL/min) were introduced to **M1** ($\phi$ = 250 μm) using syringe pumps, and the mixture was passed through **R1** ($\phi$ = 1000 μm, $L_1$ =100 cm, residence time $t^{R1}$ = 4.6 s). The resulting solution was introduced to **M2** ($\phi$ = 250 μm), where a solution of ethene-1,1-diyldibenzene (0.20 M in THF) was also introduced (flow rate: 5.0 mL/min). The resulting solution was passed through **R2** ($\phi$ = 1000 μm, $L_2$ = 100 cm, residence time $t^{R2}$ = 3.1 s). The resulting solution was introduced to **M3** ($\phi$ = 250 μm), where a solution of *tert*-butyl methacrylate (conc. in THF) was also introduced (flow rate: 5.0 mL/min). The resulting solution was passed through **R3** ($\phi$ = 1000 μm, $L_3$ = 100 cm, residence time $t^{R3}$ = 2.3 s). The resulting solution was introduced to **M4** ($\phi$ = 500 μm), where a solution of acetic aicd (1.0 M in THF) was also introduced (flow rate: 5.0 mL/min). The resulting solution was passed through **R4** ($\phi$ = 1000 μm, $L_4$ = 50 cm, residence time $t^{R4}$ = 0.9 s). After a steady state was reached, the product solution was collected for 30 seconds. To the aliquot, sat. $NH_4Cl$ aq. was added, and then the organic phase was analyzed by NMR and GPC.

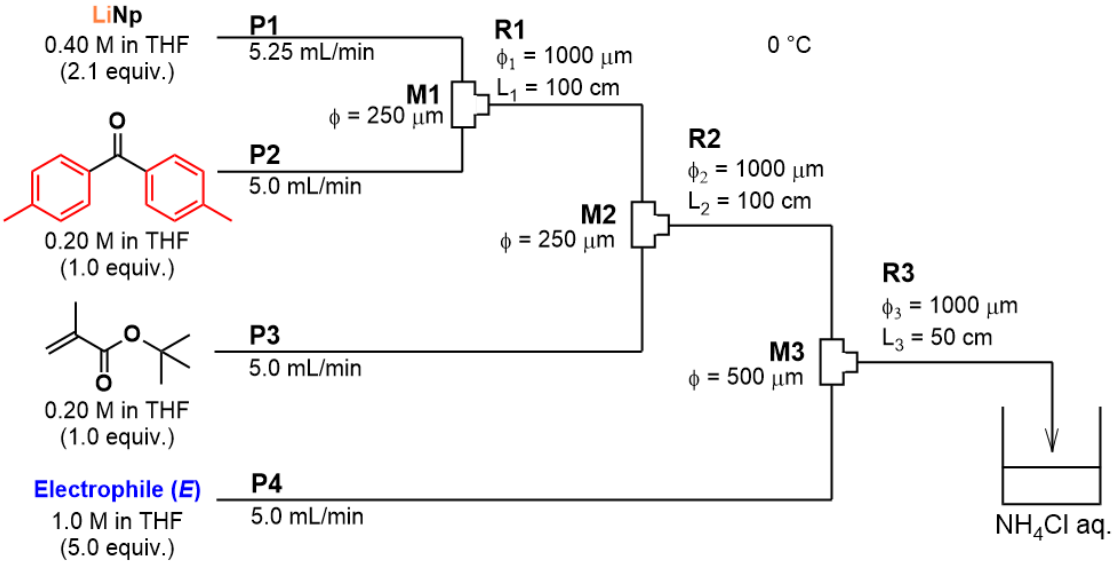



**tert-butyl 6-hydroxy-2-methyl-4,4-diphenyl-6,6-di-p-tolylhexanoate (28) :** Obtained from methyl methacrylate (**14**) of 0.2 M (1.0 equiv.) as the concentration of solution in 50% yield (NMR yield). Yields were determined by NMR analysis using an internal standard (dimethyl terephthalate). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 38% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.35 (d, $J$ = 8.0 Hz, 2H), 7.26-7.13 (m, 5H), 7.02-6.91 (m, 9H), 6.73 (d, $J$ = 8.4 Hz, 2H), 3.59-3.50 (m, 2H), 3.36 (dd, $J$ = 14.8, 8.4 Hz, 1H), 3.11 (d, $J$ = 14.4 Hz, 1H), 2.24 (s, 3H), 2.15 (s, 3H), 2.06-2.04 (m, 1H), 1.80 (d, $J$ = 14.0 Hz, 1H), 1.13 (s, 9H), 0.76 (d, $J$ = 7.6 Hz, 3H); $^{13}$C NMR (100MHz, $CDCl_3$) δ 177.9, 149.9, 148.8, 146.5, 144.3, 135.4, 134.1, 129.0 (2C), 128.6 (2C), 128.0 (4C), 127.8 (2C), 127.0 (2C), 125.7, 125.3, 125.0 (2C), 124.9 (2C), 80.4, 76.6, 49.1, 47.5, 41.9, 36.8, 27.6 (3C), 20.8, 20.7, 20.6. HRMS (ESI) *m/z* Calcd for $C_{37}H_{42}O_3Na$ $[M+Na]^+$ 557.3032; Found: 557.3020.

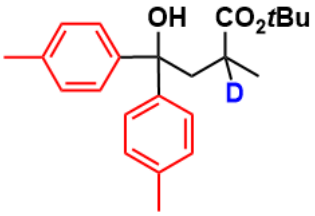



**oligomer 29:** The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.34-7.21 (m, 7H), 6.96-6.61 (m, 11H), 3.72 (m, 1H), 3.14-3.11 (m, 1H), 2.36-1.83 (m, 151H), 1.44-1.41 (m, 802H), 1.18-1.01 (m, 244H). GPC $M_n$: 3.4 x $10^3$, PDI:1.06.

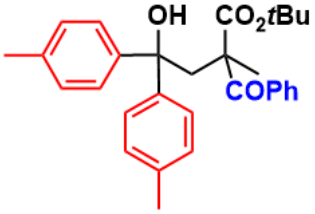
### 3-5-10. Synthesis of monoaddition product trapped by electrophiles in a flow microreactor.



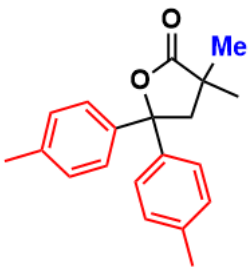

A flow microreactor system consisting of three T-shaped micromixers (**M1**, **M2** and **M3**), three microtube reactors (**R1**, **R2** and **R3**), and four pre-cooling units was used in a cooling bath at 0 °C (**P1** (L = 100 cm) and **P2** (100 cm) and **P3** (100 cm) and **P4** (50 cm)). A solution of lithium naphthalenide (0.40 M in THF, flow rate: 5.25 mL/min) and a solution of 4,4'-Dimethylbenzophenone (0.20 M in THF, flow rate: 5.0 mL/min) were introduced to **M1** ($\phi$ = 250 μm) using syringe pumps, and the mixture was passed through **R1** ($\phi$ = 1000 μm, 100 cm, residence time $t^{R1}$ = 4.6 s). The resulting solution was introduced to **M2** ($\phi$ = 250 μm), where a solution of *tert*-butyl methacrylate (0.20 M in THF) was also introduced (flow rate: 5.0 mL/min). The resulting solution was passed through **R2** ($\phi$ = 1000 μm, L = 100 cm, residence time = 3.1 s). The resulting solution was introduced to **M3** ($\phi$ = 500 μm), where a solution of electrophile (1.0 M in THF) was also introduced (flow rate: 5.0 mL/min). The resulting solution was passed through **R3** ($\phi$ = 1000 μm, L = 50 cm, residence time = 1.2 s). After a steady state was reached, the product solution was collected for 30 seconds. To the aliquot, sat. $NH_4Cl$ aq. was added, and then the organic phase was analyzed by NMR.



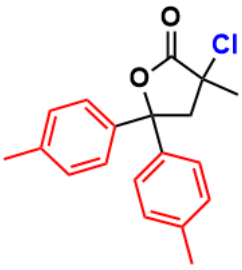

**tert-butyl 4-hydroxy-2-methyl-4,4-di-p-tolylbutanoate-2-d (30) :** Obtained from methanol-d as the electrophile in 91% yield and the deuteration in 99% (NMR yield). Yields were determined by NMR analysis using an internal standard (dimethyl terephthalate). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 75% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.30 (dt, *J* = 8.4, 2.4 Hz, 4H), 7.10 (t, *J* = 8.4 Hz, 4H), 2.99 (broad, 1H), 2.73 (dd, *J* = 14.0, 2.4 Hz, 1H), 2.32-2.26 (m, 7H), 1.43 (m, 9H), 1.10 (m, 3H); $^{13}$C NMR (100MHz, $CDCl_3$) δ 177.6, 145.4, 143.2, 136.3, 135.9, 128.7 (4C), 125.9 (2C), 125.8 (2C), 80.3, 77.5, 45.1, 36.1, 27.9 (3C), 21.0, 20.9, 19.4. HRMS (ESI) *m/z* Calcd for $C_{23}H_{29}O_3DNa$ $[M+Na]^+$ 378.2150; Found: 378.2144.




**tert-butyl 2-benzoyl-4-hydroxy-2-methyl-4,4-di-p-tolylbutanoate (31) :** Obtained from benzoyl chloride as the electrophile in 72% yield (NMR yield). Yields were determined by NMR analysis using an internal standard (dimethyl terephthalate). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 56% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.73-7.71 (m, 2H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.41 (d, *J* = 8.4 Hz, 2H), 7.37-7.35 (m, 3H), 7.15 (d, *J* = 8.4 Hz, 2H), 7.03 (d, *J* = 7.6 Hz, 2H), 3.77 (d, *J* = 12.8 Hz, 1H), 3.26 (broad, 1H), 3.03 (d, *J* = 12.8 Hz, 2H), 2.31 (s, 3H), 2.24 (s, 3H), 1.41 (s, 9H), 0.77 (s, 3H); $^{13}$C NMR (100MHz, $CDCl_3$) δ 172.5, 147.3, 145.1, 139.9, 135.9, 135.6, 129.0 (2C), 128.8 (2C), 128.3, 128.1 (2C), 127.1 (2C), 124.7 (4C), 107.6, 86.1, 81.1, 58.1, 47.0, 27.8 (3C), 22.2, 20.9, 20.8. HRMS (ESI) *m/z* Calcd for $C_{30}H_{34}O_4Na$ $[M+Na]^+$ 481.2349; Found: 481.2345.



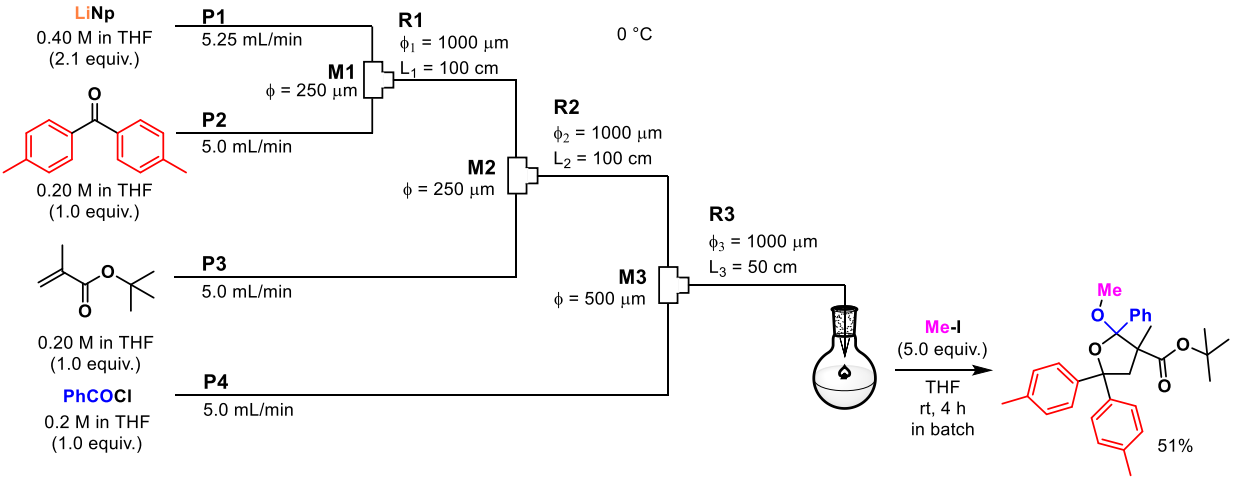

**3,3-dimethyl-5,5-di-p-tolyldihydrofuran-2(3H)-one (32) :** Obtained from methyl trifluoromethanesulfonate as the electrophile in 75% yield (NMR yield). Yields were determined by NMR analysis using an internal standard (dimethyl terephthalate). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 61% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.4 Hz, 4H), 7.14 (d, *J* = 6.4 Hz, 4H), 2.88 (s, 2H), 2.30 (s, 6H), 1.14 (s, 6H); $^{13}$C NMR (100MHz, $CDCl_3$) δ 181.3, 141.9 (2C), 137.1 (2C), 129.1 (4C), 124.8 (4C), 86.1, 49.8, 40.5, 25.7 (2C), 20.9 (2C). HRMS (ESI) *m/z* Calcd for $C_{20}H_{23}O_2$ $[M+H]^+$ 295.1693; Found: 295.1690.



**3-chloro-3-methyl-5,5-di-p-tolyldihydrofuran-2(3H)-one (33) :** Obtained from perchloromethane as the electrophile in 52% yield (NMR yield). Yields were determined by NMR analysis using an internal standard (dimethyl terephthalate). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 41% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.32 (d, $J$ = 8.4 Hz, 2H), 7.27-7.25 (m, 2H), 7.14 (d, $J$ = 8.4 Hz, 4H), 3.55 (d, $J$ = 14.4 Hz, 1H), 3.18 (d, $J$ = 14.0 Hz, 1H), 2.31 (d, $J$ = 2.0 Hz, 6H), 1.73 (s, 3H); $^{13}$C NMR (100MHz, $CDCl_3$) δ 173.7, 140.9, 139.9, 137.9, 137.7, 129.5 (2C), 129.3 (2C), 125.1 (2C), 124.9 (2C), 87.2, 62.5, 52.1, 27.7, 21.1 (2C). HRMS (ESI) *m/z* Calcd for $C_{19}H_{19}O_2ClNa$ $[M+Na]^+$ 337.0966; Found: 337.0957.

### 3-5-11. Trapping of the Cyclized Intermediate by Methylation in a flow microreactor

#### 3-5-11-1. Experimental Procedure

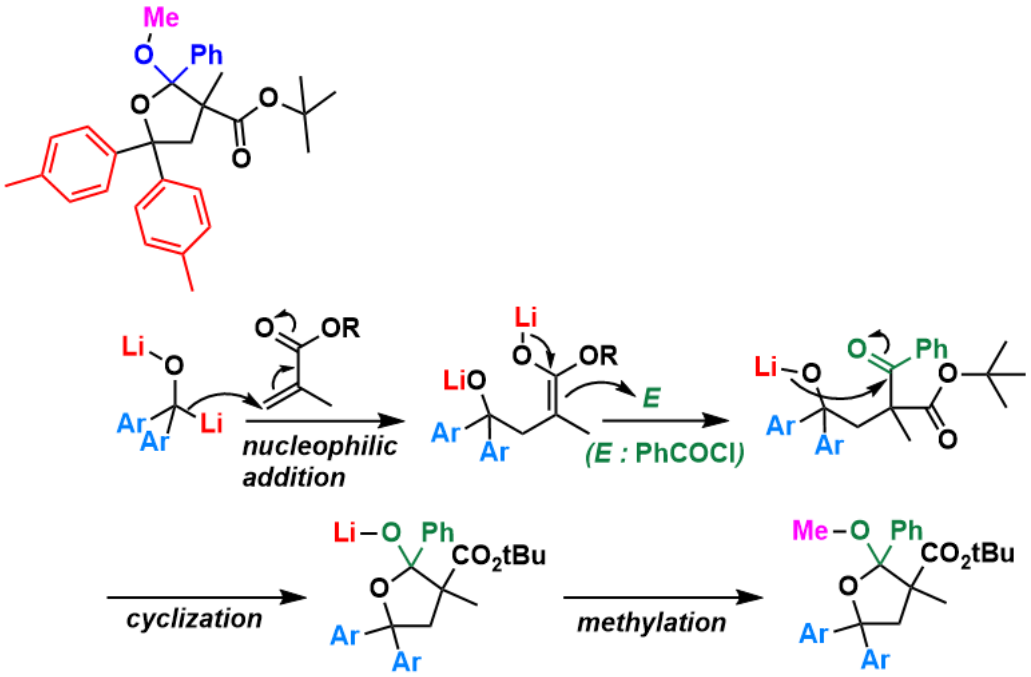



A flow microreactor system consisting of three T-shaped micromixers (**M1**, **M2** and **M3**), three microtube reactors (**R1**, **R2** and **R3**), and four pre-cooling units was used in a cooling bath at 0 °C (**P1** (L = 100 cm) and **P2** (100 cm) and **P3** (100 cm) and **P4** (50 cm)). A solution of lithium naphthalenide (0.40 M in THF, flow rate: 5.25 mL/min) and a solution of 4,4'-dimethylbenzophenone (0.20 M in THF, flow rate: 5.0 mL/min) were introduced to **M1** (ϕ = 250 μm) using syringe pumps, and the mixture was passed through **R1** (ϕ = 1000 μm, 100 cm, residence time $t^{R1}$ = 4.6 s). The resulting solution was introduced to **M2** (ϕ = 250 μm), where a solution of *tert*-butyl methacrylate (0.20 M in THF) was also introduced (flow rate: 5.0 mL/min). The resulting solution was passed through **R2** (ϕ = 1000 μm, L = 100 cm, residence time $t^{R2}$ = 3.1 s). The resulting solution was introduced to **M3** (ϕ = 500 μm), where a solution of benzoyl chloride (0.2 M in THF) was also introduced (flow rate: 5.0 mL/min). The resulting solution was passed through **R3** (ϕ = 1000 μm, L = 50 cm, residence time $t^{R3}$ = 1.2 s). After a steady state was

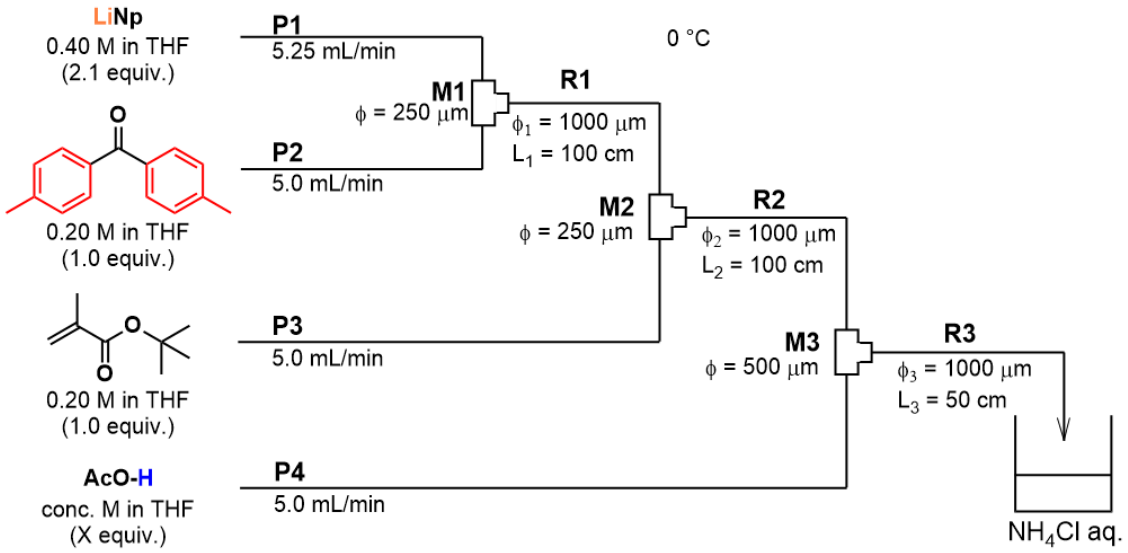
reached, the product solution was collected under an argon atmosphere for 30 s. Methyl iodide (0.16 mL, 364.8 mg, 5.0 equiv.) was added and the mixture was stirred at room temperature for 4 h. To the aliquot, sat. $NH_4Cl$ aq. was added, and then the organic phase was analyzed by NMR.

***tert*-butyl 2-methoxy-3-methyl-2-phenyl-5,5-di-p-tolyltetrahydrofuran-3-carboxylate (43)**: Obtained in 51% yield (NMR yield). Yields were determined by NMR analysis using an internal standard (1, 1, 2, 2-tetrachloroethane). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 41% isolated yield. $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.68 (broad, 1H), 7.56 (d, $J$ = 7.6 Hz, 2H), 7.42-7.31 (m, 5H), 7.14 (d, $J$ = 8.0 Hz, 2H), 7.04 (d, $J$ = 8.0 Hz, 2H), 4.00 (d, $J$ = 12.8 Hz, 1H), 2.91 (s, 3H), 2.89 (d, $J$ = 12.8 Hz, 1H), 2.29 (s, 3H), 2.24 (s, 3H), 1.44 (s, 9H), 0.68 (s, 3H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 172.0, 146.1 (2C), 136.4, 135.6 (2C), 129.4 (2C), 129.0 (2C), 128.6 (2C), 128.1, 127.1 (2C), 125.3 (2C), 124.5 (2C), 111.8, 86.1, 80.6, 58.9, 50.7, 46.1, 27.9 (3C), 22.0, 20.9 (2C). HRMS (ESI) m/z Calcd for $C_{31}H_{36}O_4Na$ [M+Na]+ 495.2506; Found: 495.2501.

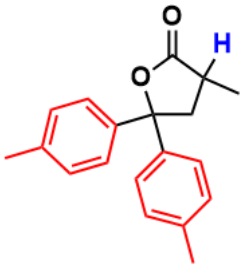
### 3-5-11-2. Proposed Mechanism



### 3-5-12. Effect of equivalents of acetic acid on anionic monoaddition of lithium BPD with *tert*-butyl methacrylate in the flow microreactor.




A flow microreactor system consisting of three T-shaped micromixers (**M1**, **M2** and **M3**), three microtube reactors (**R1**, **R2** and **R3**), and four pre-cooling units was used in a cooling bath at 0 °C (**P1** (L = 100 cm) and **P2** (100 cm) and **P3** (100 cm) and **P4** (50 cm)). A solution of lithium naphthalenide (0.40 M in THF, flow rate: 5.25 mL/min) and a solution of 4,4'-Dimethylbenzophenone (0.20 M in THF, flow rate: 5.0 mL/min) were introduced to **M1** ($\phi$ = 250 μm) using syringe pumps, and the mixture was passed through **R1** ($\phi$ = 1000 μm, $L_1$ = 100 cm, residence time $t^{R1}$ = 4.6 s). The resulting solution was introduced to **M2** ($\phi$ = 250 μm), where a solution of *tert*-Butyl methacrylate (0.20 M in THF) was also introduced (flow rate: 5.0 mL/min). The resulting solution was passed through **R2** ($\phi$ = 1000 μm, $L_2$ = 100 cm, residence time = 3.1 s). The resulting solution was introduced to **M3** ($\phi$ = 500 μm), where a solution of benzoic acid (conc. M in THF) was also introduced (flow rate: 5.0 mL/min, X equiv.). The resulting solution was passed through **R3** ($\phi$ = 1000 μm, $L_3$ = 50 cm, residence time = 1.2 s). After a steady state was reached, the product solution was collected for 30 seconds. To the aliquot, sat. $NH_4Cl$ aq. was added, and then the organic phase was analyzed by NMR.



**3-methyl-5,5-di-p-tolyldihydrofuran-2(3H)-one (40) :** The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.29 (dd, *J* = 17.2, 8.4 Hz, 4H), 7.11 (dd, *J* = 8.0, 5.2 Hz, 4H), 3.16 (dd, *J* = 12.4, 7.6 Hz, 1H), 2.68-2.56 (m, 1H), 2.40 (t, *J* = 12, 1H), 2.28 (s, 6H), 1.25 (d, *J* = 7.6 Hz, 3H); $^{13}$C NMR (100MHz, $CDCl_3$) δ 178.7, 141.0, 139.7, 137.3 (2C), 129.1 (2C), 128.9 (2C), 125.0 (4C), 87.1, 43.7, 35.0, 20.8 (2C), 14.5. HRMS (ESI) *m/z* Calcd for $C_{19}H_{21}O_2$ $[M+H]^+$ 281.1536;

Found: 281.1528.

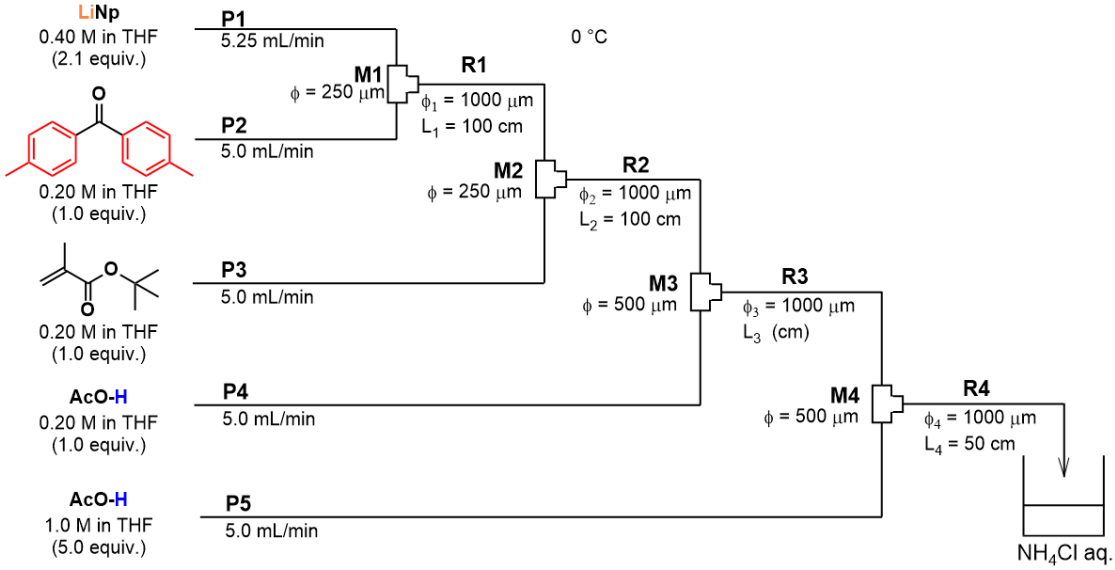
**Table 12.** investigation for the structure of monoadduct on equivalent of HOAc.

| | AcO-H | | yield (%) | |
|---|---|---|---|---|
| Entry | Conc, (M) | equiv. (X) | **Chain (4)** | **Ring (40)** |
| 1 | 0.2 | 1.0 | 53 | 40 |
| 2 | 0.4 | 2.0 | 96 | - |
| 3 | 0.6 | 3.0 | 93 | - |
| 4 | 1.0 | 5.0 | 96 | - |

Yields were determined by $^{1}$H NMR analysis using an internal standard (dimethyl terephthalate).

### 3-5-13. Effect of retention times on anionic monoaddition of lithium BPD with *tert*-butyl methacrylate under the quenching by 1.0 equivalent of HOAc in the flow microreactor.

#### 3-5-11-1. Lithium Naphthalenide (LiNp)



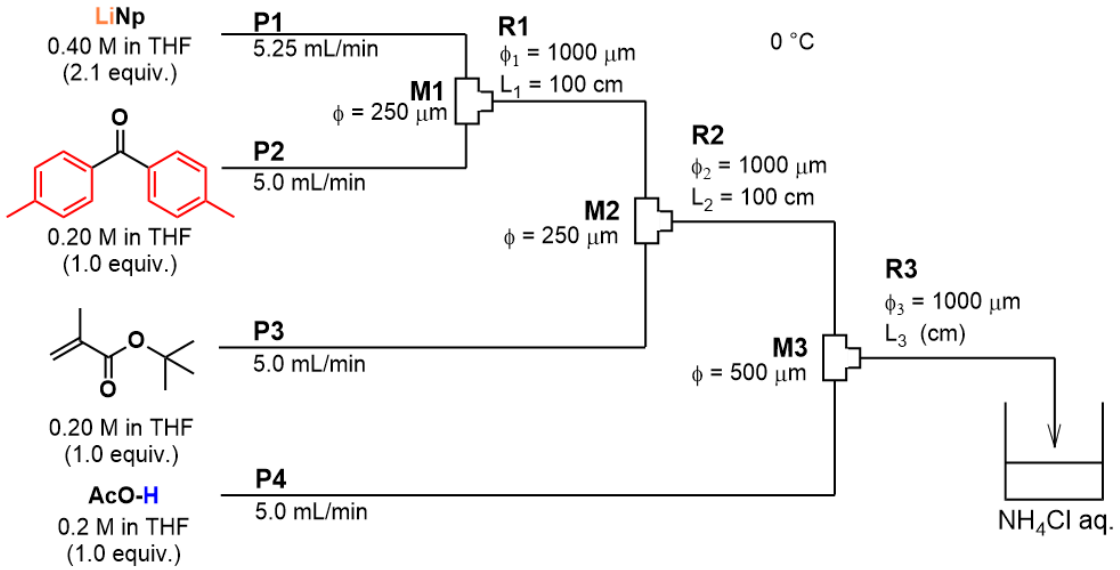

A flow microreactor system consisting of four T-shaped micromixers (**M1**, **M2, M3** and **M4**), four microtube reactors (**R1**, **R2, R3** and **R4**), and five pre-cooling units was used in a cooling bath at 0 °C (**P1** (L = 100 cm) and **P2** (100 cm) and **P3** (100 cm) and **P4** (100 cm) and **P5** (100 cm)). A solution of lithium naphthalenide (0.40 M in THF, flow rate: 5.25 mL/min) and a solution of 4,4'-Dimethylbenzophenone (0.20 M in THF, flow rate: 5.0 mL/min) were introduced to **M1** ($\phi$ = 250 μm) using syringe pumps, and the mixture was passed through **R1** ($\phi$ = 1000 μm, $L_1$ =100 cm, residence time = 4.6 s). The resulting solution was introduced to **M2** ($\phi$ = 250 μm),

where a solution of *tert*-butyl methacrylate (0.20 M in THF) was also introduced (flow rate: 5.0 mL/min). The resulting solution was passed through **R2** ($\phi$ = 1000 μm, $L_2$ = 100 cm, residence time = 3.1 s). The resulting solution was introduced to **M3** ($\phi$ = 500 μm), where a solution of acetic acid (0.20 M in THF) was also introduced (flow rate: 5.0 mL/min). The resulting solution was passed through **R3** ($\phi$ = 1000 μm, $L_3$ (cm), residence time = *t*). The resulting solution was introduced to **M4** ($\phi$ = 500 μm), where a solution of acetic aicd (1.0 M in THF) was also introduced (flow rate: 5.0 mL/min). The resulting solution was passed through **R4** ($\phi$ = 1000 μm, $L_4$ = 50 cm, residence time *t* = 0.9 s). After a steady state was reached, the product solution was collected for 30 seconds. To the aliquot, sat. $NH_4Cl$ aq. was added, and then the organic phase was analyzed by NMR.

**Table 13.** investigation for the structure of monoadduct on residence time with 2.1 equivalents of lithium naphthalenide and 1.0 equivalent of HOAc.

| entry | $L_3$ (cm) | ***t*** (second) | yield (%) | |
|---|---|---|---|---|
| | | | **Chain (4)** | **Ring (40)** |
| 1 | 3.5 | 0.1 | 81 | 9 |
| 2 | 50 | 1.2 | 52 | 40 |

Yields were determined by 1H NMR analysis using an internal standard (dimethyl terephthalate).




A flow microreactor system consisting of three T-shaped micromixers (**M1**, **M2** and **M3**), three microtube reactors (**R1**, **R2** and **R3**), and four pre-cooling units was used in a cooling bath at 0 °C

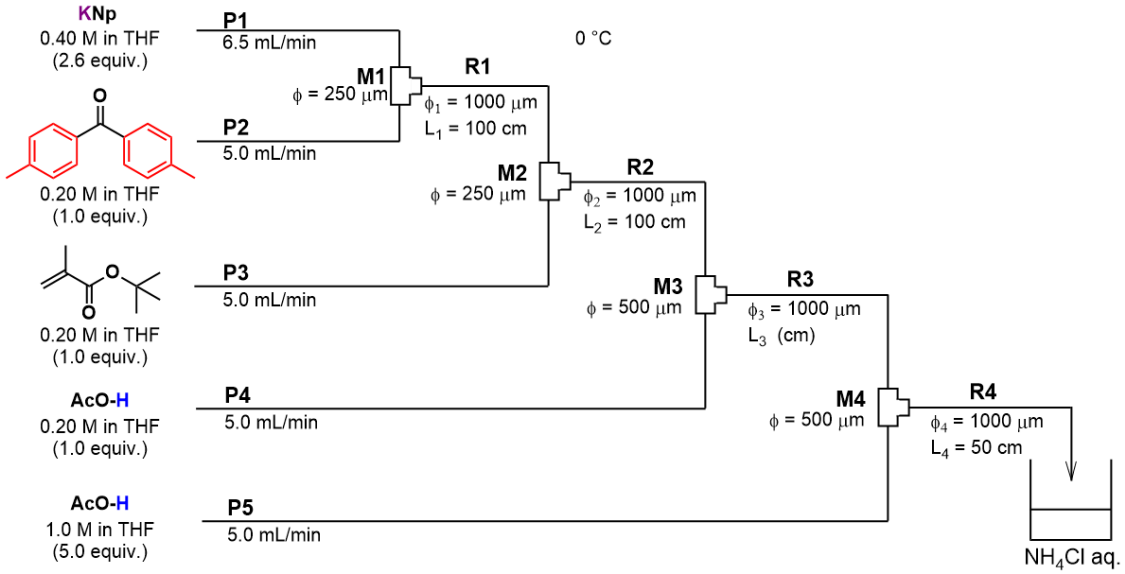
(**P1** (L = 100 cm) and **P2** (100 cm) and **P3** (100 cm) and **P4** (100 cm)). A solution of lithium naphthalenide (0.40 M in THF, flow rate: 5.25 mL/min) and a solution of 4,4'-Dimethylbenzophenone (0.20 M in THF, flow rate: 5.0 mL/min) were introduced to **M1** ($\phi$ = 250 μm) using syringe pumps, and the mixture was passed through **R1** ($\phi$ = 1000 μm, $L_1$ = 100 cm, residence time $t^{R1}$ = 4.6 s). The resulting solution was introduced to **M2** ($\phi$ = 250 μm), where a solution of *t*-Butyl methacrylate (0.20 M in THF) was also introduced (flow rate: 5.0 mL/min). The resulting solution was passed through **R2** ($\phi$ = 1000 μm, $L_2$ = 100 cm, residence time = 3.1 s). The resulting solution was introduced to **M3** ($\phi$ = 500 μm), where a solution of acetic acid (0.2 M in THF) was also introduced (flow rate: 5.0 mL/min). The resulting solution was passed through **R3** ($\phi$ = 1000 μm, $L_3$ = 50 ~ 400 cm, residence time = 1.2 ~ 18.6 s). After a steady state was reached, the product solution was collected for 30 seconds. To the aliquot, sat. $NH_4Cl$ aq. was added, and then the organic phase was analyzed by NMR.

**Table 14.** investigation for the structure of monoadduct on residence time with 2.1 equivalents of lithium naphthalenide and 1.0 equivalent of HOAc.

| entry | $L_3$ (cm) | ***t*** (second) | yield (%) | |
|---|---|---|---|---|
| | | | **Chain (4)** | **Ring (40)** |
| 1 | 50 | 1.2 | 81 | 9 |
| 2 | 400 | 9.3 | 52 | 40 |
| 3[1)] | 50 | >60 | 4 | 88 |

Yields were determined by 1H NMR analysis using an internal standard (dimethyl terephthalate).
[1)] After the product solution was collected for 30 seconds, Stirred for 1 min at 0 °C in batch reactor

### 3-5-11-1. Potassium Naphthalenide (KNp)

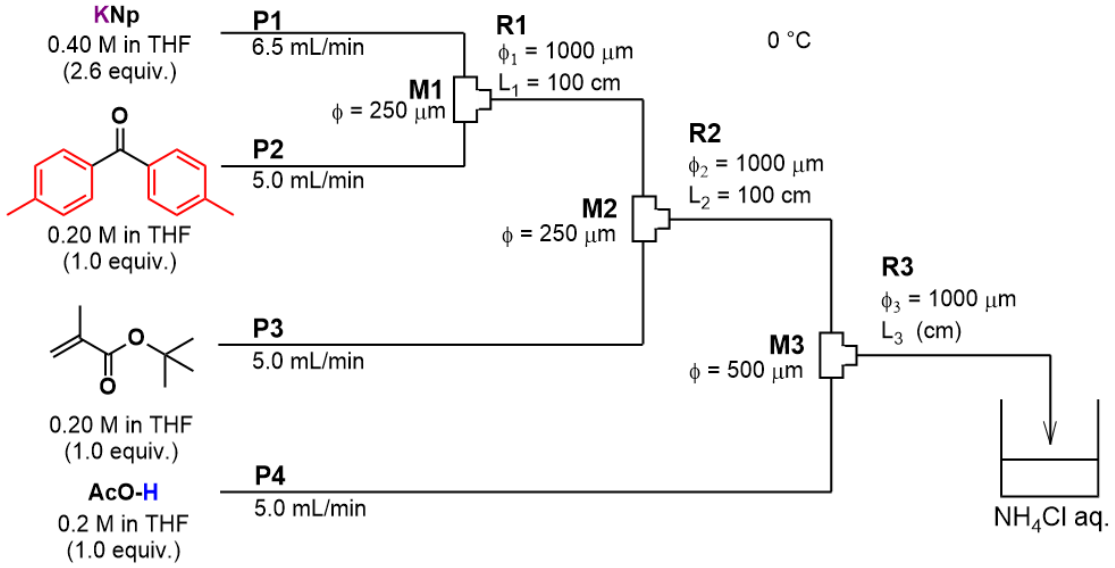



A flow microreactor system consisting of four T-shaped micromixers (**M1**, **M2, M3** and **M4**), four microtube reactors (**R1**, **R2, R3** and **R4**), and five pre-cooling units was used in a cooling bath at 0 °C (**P1** (L = 100 cm) and **P2** (100 cm) and **P3** (100 cm) and **P4** (100 cm) and **P5** (100 cm)). A solution of potassium naphthalenide (0.40 M in THF, flow rate: 6.5 mL/min) and a solution of 4,4'-Dimethylbenzophenone (0.20 M in THF, flow rate: 5.0 mL/min) were introduced to **M1** ($\phi$ = 250 μm) using syringe pumps, and the mixture was passed through **R1** ($\phi$ = 1000 μm, $L_1$ =100 cm, residence time = 4.1 s). The resulting solution was introduced to **M2** ($\phi$ = 250 μm), where a solution of *tert*-butyl methacrylate (0.20 M in THF) was also introduced (flow rate: 5.0 mL/min). The resulting solution was passed through **R2** ($\phi$ = 1000 μm, $L_2$ = 100 cm, residence time = 2.9 s). The resulting solution was introduced to **M3** ($\phi$ = 500 μm), where a solution of acetic acid (0.20 M in THF) was also introduced (flow rate: 5.0 mL/min). The resulting solution was passed through **R3** ($\phi$ = 1000 μm, $L_3$ (cm), residence time = *t*). The resulting solution was introduced to **M4** ($\phi$ = 500 μm), where a solution of acetic aicd (1.0 M in THF) was also introduced (flow rate: 5.0 mL/min). The resulting solution was passed through **R4** ($\phi$ = 1000 μm, $L_4$ = 50 cm, residence time *t* = 0.9 s). After a steady state was reached, the product solution was collected for 30 seconds. To the aliquot, sat. $NH_4Cl$ aq. was added, and then the organic phase was analyzed by NMR.

**Table 15.** investigation for the structure of monoadduct on residence time with 2.6 equivalents of potassium naphthalenide 1.0 equivalent of HOAc.

| entry | $L_3$ (cm) | *t* (second) | yield (%) | |
|---|---|---|---|---|
| | | | **Chain (4)** | **Ring (40)** |
| 1 | 3.5 | 0.1 | - | 52 |
| 2 | 50 | 1.1 | - | 52 |

Yields were determined by 1H NMR analysis using an internal standard (dimethyl terephthalate).




A flow microreactor system consisting of three T-shaped micromixers (**M1**, **M2** and **M3**), three microtube reactors (**R1**, **R2** and **R3**), and four pre-cooling units was used in a cooling bath at 0 °C (**P1** (L = 100 cm) and **P2** (100 cm) and **P3** (100 cm) and **P4** (100 cm)). A solution of potassium naphthalenide (0.40 M in THF, flow rate: 6.5 mL/min) and a solution of 4,4'-Dimethylbenzophenone (0.20 M in THF, flow rate: 5.0 mL/min) were introduced to **M1** ($\phi$ = 250 μm) using syringe pumps, and the mixture was passed through **R1** ($\phi$ = 1000 μm, $L_1$ = 100 cm, residence time = 4.1 s). The resulting solution was introduced to **M2** ($\phi$ = 250 μm), where a solution of *t*-Butyl methacrylate (0.20 M in THF) was also introduced (flow rate: 5.0 mL/min). The resulting solution was passed through **R2** ($\phi$ = 1000 μm, $L_2$ = 100 cm, residence time = 2.9 s). The resulting solution was introduced to **M3** ($\phi$ = 500 μm), where a solution of acetic acid (0.2 M in THF) was also introduced (flow rate: 5.0 mL/min). The resulting solution was passed through **R3** ($\phi$ = 1000 μm, $L_3$ = 50 ~ 800 cm, residence time = 1.1 ~ 17.5 s). After a steady state

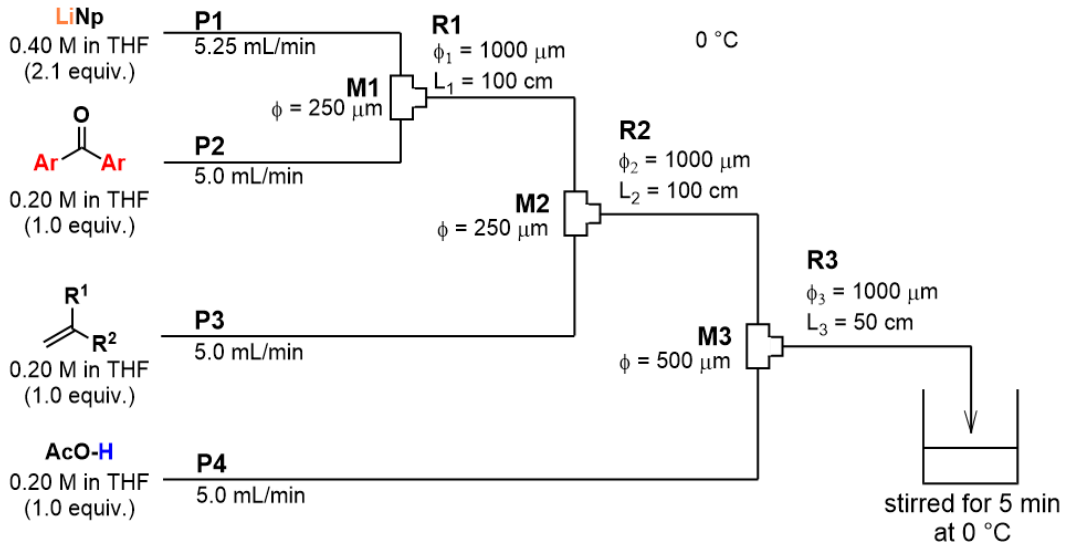
was reached, the product solution was collected for 30 seconds. To the aliquot, sat. $NH_4Cl$ aq. was added, and then the organic phase was analyzed by NMR.

**Table 16.** investigation for the structure of monoadduct on residence time with 2.6 equivalents of potassium naphthalenide 1.0 equivalent of HOAc.

| entry | $L_3$ (cm) | *t* (second) | yield (%) | |
|---|---|---|---|---|
| | | | **Chain (4)** | **Ring (40)** |
| 1 | 50 | 1.1 | - | 52 |
| 2 | 400 | 8.8 | - | 50 |

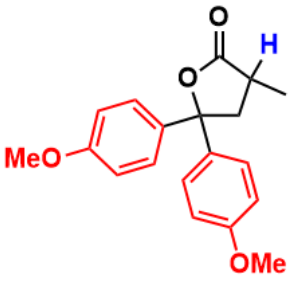
Yields were determined by 1H NMR analysis using an internal standard (dimethyl terephthalate).

### 3-5-14. Synthesis of ring-type monoaddition product via benzophenone's derivatives and methacrylates in a flow microreactor.

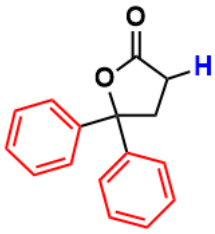



A flow microreactor system consisting of three T-shaped micromixers (**M1**, **M2** and **M3**), three microtube reactors (**R1**, **R2** and **R3**), and four pre-cooling units was used in a cooling bath at 0 °C (**P1** (L = 100 cm) and **P2** (100 cm) and **P3** (100 cm) and **P4** (100 cm)). A solution of lithium naphthalenide (0.40 M in THF, flow rate: 5.25 mL/min) and a solution of benzophenone's derivative (0.20 M in THF, flow rate: 5.0 mL/min) were introduced to **M1** ($\phi$ = 250 μm) using syringe pumps, and the mixture was passed through **R1** ($\phi$ = 1000 μm, 100 cm, residence time = 4.6 s). The resulting solution was introduced to **M2** ($\phi$ = 250 μm), where a solution of vinyl monomer (0.20 M in THF) was also introduced (flow rate: 5.0 mL/min). The resulting solution

was passed through **R2** ($\phi$ = 1000 μm, L = 100 cm, residence time = 3.1 s). The resulting solution was introduced to **M3** ($\phi$ = 500 μm), where a solution of electrophile (1.0 M in THF) was also introduced (flow rate: 5.0 mL/min). The resulting solution was passed through **R3** ($\phi$ = 1000 μm, L = 50 cm, residence time = 1.2 s). After a steady state was reached, the product solution was collected for 30 seconds. Then, the product solution was stirred for 5 min at 0 °C in batch reactor. To the aliquot, sat. $NH_4Cl$ aq. was added, and then the organic phase was analyzed by NMR.




**5,5-bis(4-methoxyphenyl)-3-methyldihydrofuran-2(3H)-one (41) :** Obtained from bis(4-methoxyphenyl)methanone and methyl methacrylate as the benzophenone's derivative and vinyl monomer in 53% yield (NMR yield). Yields were determined by NMR analysis using an internal standard (dimethyl terephthalate). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 40% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.35-7.31 (m, 2H), 7.29-7.26 (m, 2H), 6.88-6.82 (m, 4H), 3.77 (d, $J$ = 3.2 Hz, 6H), 3.14 (dd, $J$ = 12.4, 7.6 Hz, 1H), 2.72-2.62 (m, 1H), 2.41 (t, $J$ = 12.4 Hz, 1H), 1.28 (d, $J$ = 6.8 Hz, 3H); $^{13}$C NMR (100MHz, $CDCl_3$) δ 179.0, 159.1 (2C), 136.4, 134.9, 126.8 (4C), 114.0 (2C), 113.8 (2C), 87.3, 55.4 (2C), 44.1, 35.5, 14.8. HRMS (ESI) *m/z* Calcd for $C_{19}H_{21}O_4$ $[M+H]^+$ 313.1440; Found:313.1430.




**5,5-diphenyldihydrofuran-2(3H)-one (42) :** Obtained from bis(4-methoxyphenyl)methanone and methyl methacrylate as the benzophenone's derivative and vinyl monomer in 86% yield (NMR yield). Yields were determined by NMR analysis using an internal standard (dimethyl terephthalate). The spectral data were identical to those of reported in the literature.[1)]

# Chapter 4

# Flash-Flow Generation and Selective Monoaddition of Organo-potassium Species to Lactones

## 4-1. Introduction

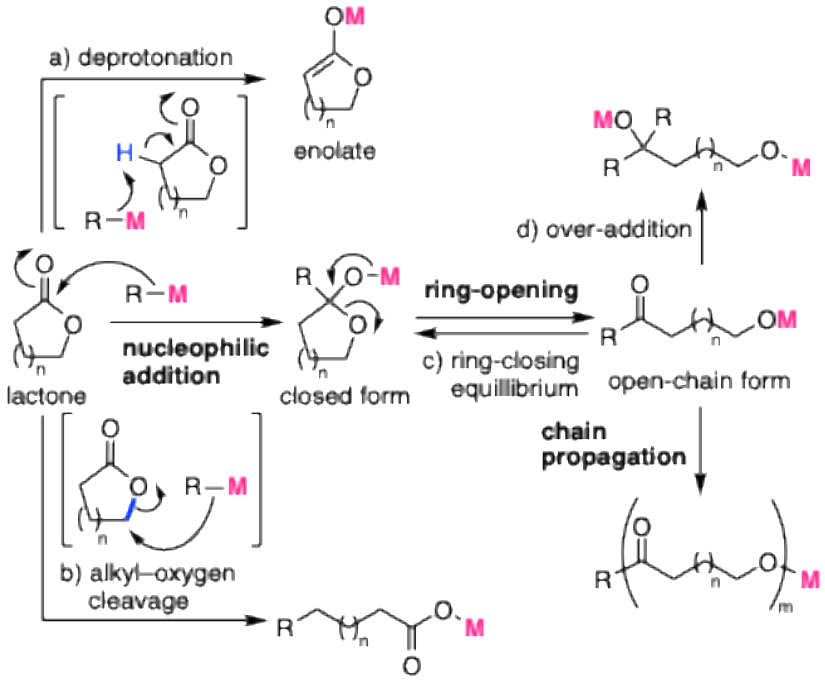
Sustainable development goals for future chemical industries nowadays requires the reusable and environmentally benign materials such as biodegradable polyesters.[1,2] Polylactone synthesis by anionic ring-opening polymerization is recognized as one of the promising candidates for the controlled polymerization giving highly dispersed polymers composed of single or multiple monomer units.[3] Various organic bases[4] and metal alkoxides[5] have been utilized for the ring-opening polymerization of lactones for these purposes. On the other hand, during such polymerization pathways, backbiting of the anionic intermediates to quench the polymerization and cleave the elongating polymer chain could be a major problem for disturbing the well-controlled polymerization. Furthermore, most of the initiating reagents are based on the alkoxide bases, which could not differentiate the rate of initiation and subsequent propagation steps sufficiently. Thus, terminal functionalization of both initiating and terminating reagents has not been well-studied in terms of precise synthesis of sequence-defined oligomers. Therefore, to ensure the introduction of the terminal functional groups, the author assumed that the employment of variously functionalized arylmetal nucleophiles composed of alkali metals as anionic initiators would be useful polymerization processes.[6]

Several issues may hinder selective addition–ring-opening reactions of lactones (Scheme 1). First, during the addition of a nucleophile to lactones, the strong basicity of the nucleophile can lead to the formation of enolates through α-deprotonation as a side reaction, often making precise control of the initiation reaction and the introduction of terminal substituents challenging. Second, the alkoxide terminals generated by ring opening do not merely add to the next lactone to polymerize in a chain-like manner through further addition–ring-opening reaction to lactones, but can also reversibly close the ring with the carbonyl group within the molecule. This step can become rate-limiting, leading to a decrease in polymerization growth rate and potentially contributing to side reactions. Furthermore, the carbonyl groups obtained through addition may undergo further addition of anionic nucleophiles to convert into alcohols, potentially complicating the reaction. Considering these side reactions and the resting state, it is evident that the development of a fast anionic addition-ring-opening polymerization reaction capable of achieving selective initiation and growth reactions requires highly precise reaction control techniques.[7,8]

In this context, continuous-flow synthesis has emerged as a key approach that intrinsically

supports sustainability in chemical manufacturing.[10] The intensified heat- and mass-transfer under flow conditions enables fast, selective transformations with short residence times, which translates into lower energy input for temperature control and improved reproducibility.[10e,f] Operating at steady state further reduces solvent use and waste generation through precise stoichiometric delivery and narrow hold-up volumes, and these benefits can be quantified with green metrics such as E-factor and process mass intensity (PMI).[10a] Moreover, microreactor-based flow platforms enhance the safe handling of highly reactive anionic species exemplified by organolithium chemistry.[10c,d] Implementing reactive centers based on earth-abundant alkali metals (e.g., potassium) reduces reliance on precious or supply-risk metals. Finally, continuous-flow ring-opening polymerization benefits from accelerated kinetics, narrower dispersity, and facile scale-out/scale-up, supporting more resource-efficient synthesis of well-defined polyesters and sequence-controlled oligomers [10b,f].

**Scheme 1**. Anionic ring-opening polymerization of lactones including possible side reactions.



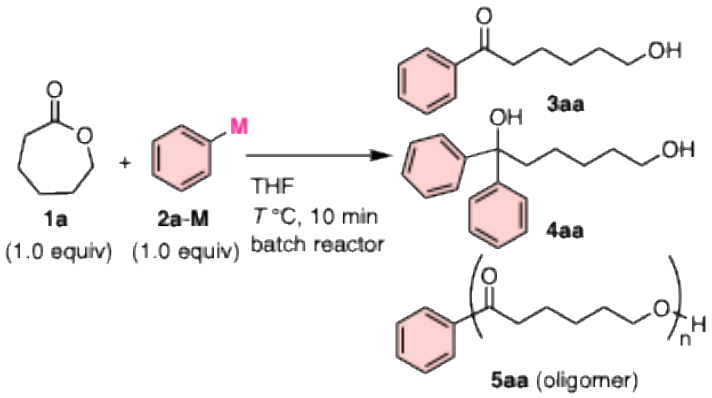

Considering this situation, the author has continuously studied on selective flow synthesis reactions with a focus on the development of organometallic carbon nucleophiles, particularly those with high reactivity, such as organolithium species.[9] Furthermore, as highly reactive chemical species, the author has recently reported the generation of short-lived organopotassium species that can be utilized for fast anionic addition through reductive potassiation or the

formation of complex aggregates with organopotassium superbases, and their application in selective reactions.[11,12] In this study, we report a precise synthetic method for functionalized ω-hydroxyketones via monomeric addition accompanied by ring-opening reaction of polymerizable lactones using flash-flow organopotassium reactions and demonstrated its application to the synthesis of sequence-controlled oligomers.[13,14]

## 4-2. Results and Discussion

As an initial attempt, the author investigated the addition–ring-opening reaction of various phenylmetal reagents with a lactone at a 1:1 molar ratio under batch conditions (Table 1). ε-Caprolactone (**1a**) was dissolved in THF, and phenylmetal species were added at temperatures of 0 °C or –78 °C, followed by a 10-minute reaction (see Supporting Information for details). When using PhMgBr, 96% of lactone **1a** was consumed at 0 °C, yielding the desired product, ω-hydroxyketone **3aa**, in a moderate yield of 64% (Entry 1). However, when the reaction was conducted at –78 °C, the reactivity significantly decreased, with only 30% of the starting material consumed and the yield of product **3aa** remaining at 16% (Entry 2). On the other hand, the reactivity of PhLi was very high with nearly complete consumption of the reactants (Entries 3 and 4). However, under these conditions, the formation of excessive arylation product **4aa** and oligomerization product **5aa** became dominant, leading to a significant decrease in the yield of desired product **3aa**. Based on these results, the author hypothesized that achieving a fast 1:1 addition reaction through immediate mixing could improve reaction selectivity and the yield of the desired product. Therefore, the author attempted to optimize the reaction conditions using a flow microreactor.

**Table 1**. Investigations for Anionic addition of arylmetal reagents in batch reactor system.[a]




| Entry | Ph-M | *T* (°C) | **1a** conv (%) | Yield (%) [b] | | |
|---|---|---|---|---|---|---|
| | | | | **3aa** | **4aa** | **5aa** |
| 1 | PhMgBr[c] | 0 | 96 | 64 | 19 | 16 |
| 2 | | –78 | 30 | 5 | 2 | 3 |
| 3 | PhLi[d] | 0 | 98 | 5 | 31 | 62 |
| 4 | | –78 | 79 | 34 | 27 | 6 |

[a] To a solution of *ε*-caprolactone (**1a**; 0.40 mmol) in THF was added Ph–M solution (0.40 mmol) dropwise at *T* °C and stirred for 10 min at this temperature before quench. [b] Yields were determined by $^1$H NMR analysis using an internal standard (1,1,2,2-tetrachloroethane). [c] Diluted from commercially available PhMgBr in THF (0.40 mmol) [d] PhLi solution was prepared from bromobenzene (0.40 mmol) and BuLi (0.40 mmol, 0.40 M in hexane).

The author then explored the optimal microflow conditions for the ring-opening addition reactions for a few types of organometallic reagents obtained commercially or generated in situ (Scheme 2). Under the micrometer-scale mixing conditions that enable rapid mixing, several temperature ranges were examined, referencing the temperature conditions from batch reactions (Table 2).

The use of PhMgBr at relatively high temperatures above 0 °C resulted in high conversion rate of the starting material as well as the high yielding of target product **3aa**. However, by-products such as alcohol **4aa** and oligomer **5aa** were also generated in non-negligible amounts (Entries 1–3). On the other hand, at low temperatures, a decrease in raw material consumption and the yield of **3aa** was observed (Entries 4 and 5). Next, in a flow system, where rapid mixing and precise temperature control are possible, PhBr and BuLi were reacted in a flow microreactor to generate PhLi, and the ring-opening addition reaction with caprolactone was primarily carried out under low-temperature conditions (Entries 6-10). As a result, **3aa** was obtained in good yield with high

selectivity; however, there was still room for improvement in terms of starting material consumption and the formation of by-products **4aa** and **5aa**. Therefore, the author attempted to further improve chemical selectivity by using an organic potassium species with higher reactivity. PhBr, BuLi, and KO$^t$Bu were sequentially reacted in a flow microreactor to generate organopotassium mixed aggregate Ph[K] (PhLi + KO$^t$Bu) in flow, followed by the ring-opening reaction with caprolactone at temperatures ranging from 0°C to –78 °C (Entry 11–15). Lactone **1a** was completely consumed, and the formation of by-product alcohol **4aa** was suppressed. Additionally, reducing the temperature decreased the formation of oligomer **5aa**, significantly improving the reaction selectivity. To further improve selectivity, the author investigated the optimal amount of Ph[K] using a small excess (Entries 16-19). The amount of Ph[K] was gradually varied from 1.0 to 3.0, and the yield of target product **3aa** and the formation of byproducts **4aa** and **5aa** were evaluated. As a result, under conditions where 1.1 equivalents of Ph[K] were used, caprolactone was completely consumed, and **3aa** was obtained with a high yield of 99%. Additionally, the formation of byproduct **4aa** and oligomers was barely detected, demonstrating extremely high chemical selectivity. However, increasing the Ph[K] equivalent to 1.5 or higher resulted in a decrease in the yield of **3aa** and an increase in the yield of **4aa**. For example, at 3.0 equivalents, the yield of **3aa** was 68%, and that of **4aa** was 33%. Furthermore, similar equimolarity studies were conducted with PhLi, but the desired reaction selectivity was not achieved (supporting information). To compensate for the effects of side reactions when generating Ph[K] in situ within the flow microreactor, conditions using 1.1 equivalents of Ph[K] were found to be optimal, providing a balanced reaction and selectivity profile.

**Scheme 2**. Flow reaction system for anionic monoarylation to ε-caprolactone

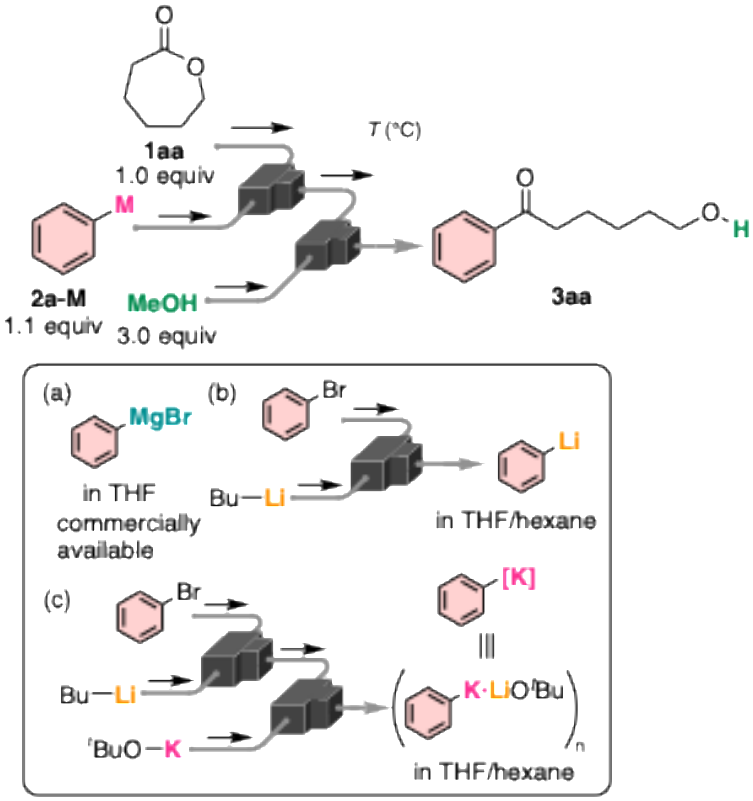



**Table 2.** Investigations for anionic addition of arylmetal reagents in flow reactor system.[a]

| Entry | Ph-M | *T* (°C) | **1a** conv (%) | Yield (%)[b] | | | Deviations from standard conditions |
|---|---|---|---|---|---|---|---|
| | | | | **3aa** | **4aa** | **5aa** | |
| 1 | PhMgBr | 40 | 90 | 60 | 15 | 13 | none |
| 2 | | 20 | 86 | 61 | 15 | 10 | |
| 3 | | 0 | 81 | 56 | 12 | 5 | |
| 4 | | –20 | 78 | 50 | 9 | 6 | |
| 5 | | –40 | 67 | 47 | 6 | 5 | |
| 6 | PhLi | 0 | 74 | 44 | 14 | 12 | |
| 7 | | –20 | 81 | 56 | 17 | 6 | |
| 8 | | –40 | 85 | 56 | 13 | 6 | |
| 9 | | –60 | 85 | 62 | 14 | 5 | |
| 10 | | –78 | 91 | 77 | 8 | 6 | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 11 | Ph[K] | 0 | 97 | 57 | trace | 36 | |
| 12 | | –20 | 100 | 62 | trace | 28 | |
| 13 | | –40 | 100 | 74 | trace | 19 | |
| 14 | | –60 | 100 | 80 | trace | 16 | |
| 15 | | –78 | 100 | 83 | trace | 9 | |
| 16 | | –78 | 100 | 99 | 1 | 0 | 1.1 equiv. Ph[K] |
| 17 | | –78 | 100 | 86 | 14 | 0 | 1.5 equiv. Ph[K] |
| 18 | | –78 | 100 | 74 | 27 | 0 | 2.0 equiv. Ph[K] |
| 19 | | –78 | 100 | 68 | 33 | 0 | 3.0 equiv. Ph[K] |
| 20 | | –78 | 100 | 64 | 12 | 18 | *F* = 12 mL/min |
| 21 | | –78 | 99 | 41 | 15 | 33 | *F* = 6 mL/min |

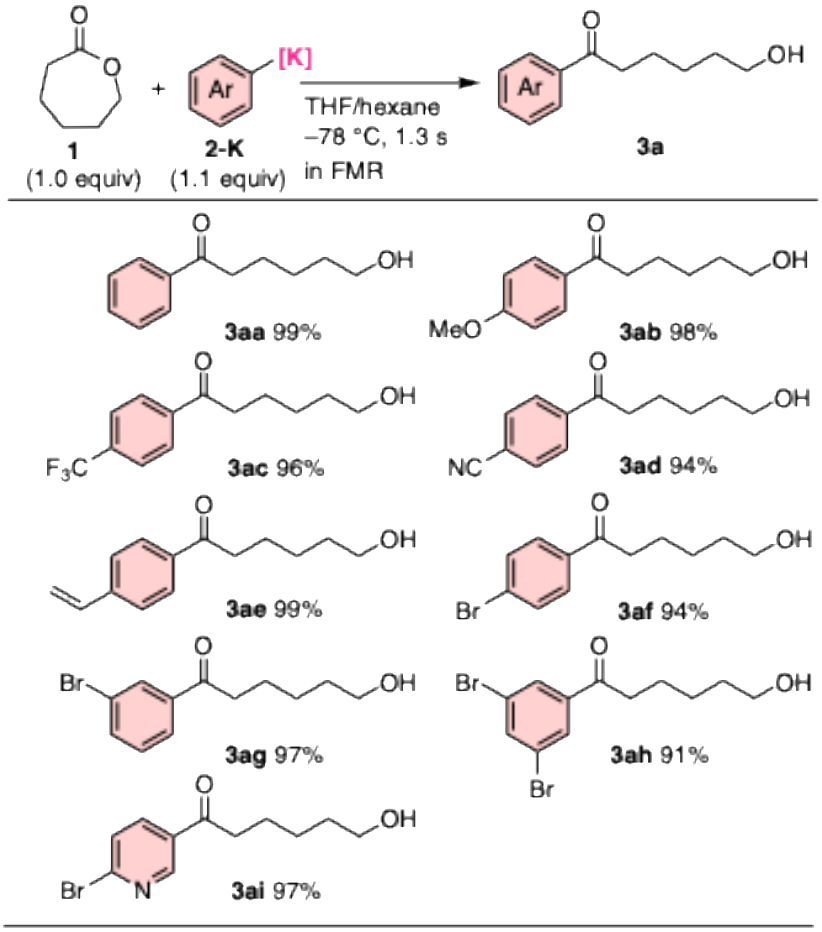
[a] ε-Caprolactone solution (**1a**; 0.20 M in THF, 1.0 equiv.) was streamed in flow and mixed with Ph–M solution (1.0 equiv.) dropwise at *T* °C and stirred for 10 min at this temperature before quench. [b] Yields were determined by $^1$H NMR analysis using an internal standard (1,1,2,2-tetrachloroethane). [c] Diluted from commercially available PhMgBr (0.40 M in THF) in THF was streamed as depicted in Scheme 2a (residence time for caprolactone addition = 12.6 s). [d] PhLi solution, prepared from bromobenzene (0.20 M in THF) and BuLi (0.40 M in hexane), was streamed as depicted in Scheme 2b (residence time for caprolactone addition = 1.6 s). [e] The PhLi solution, prepared from bromobenzene (0.20 M in THF) and BuLi (0.40 M in hexane), was then mixed with diluted KO$^t$Bu solution (0.40 M in THF, 1.0 equiv.) was streamed as depicted in Scheme 2c. Standard total flow rate *F* was 18 mL/min for the reactions with Ph[K] (residence time for caprolactone addition = 0.09 s). [f] residence time = 0.14 s. [g] residence time = 0.27 s.

By using the optimized flash synthetic system, a selective ring-opening reaction between short-lived organic potassium species controllable only within microchannels and caprolactone proceeds, enabling the high-yield synthesis of ω-hydroxyaryl ketones bearing electron-withdrawing substituents (Table 3). Aryl potassium species with electron-donating methoxy groups and strong electron-withdrawing trifluoromethyl groups can also be generated, yielding corresponding hydroxyketones **3ab** and **3ac** in high yields of 96% and 98%, respectively. This result suggests that the reaction system is less susceptible to electronic effects. Furthermore, even with aryl potassium species containing cyano groups that readily decompose in the presence of

anions or vinyl groups that may compete with anion polymerisation, the selective addition-ring-opening reaction proceeded smoothly, yielding the desired products **3ad** and **3ae** in high yields. When using dibromoarenes **1f** and **1g**, tribromoarene **1h**, and dibromopyridine **1i**, the organic potassium species formed were selectively potassiated at only one bromo group in the flash flow system, reacting with lactone **1a** to yield the products **3af**–**3ai** in high yields.

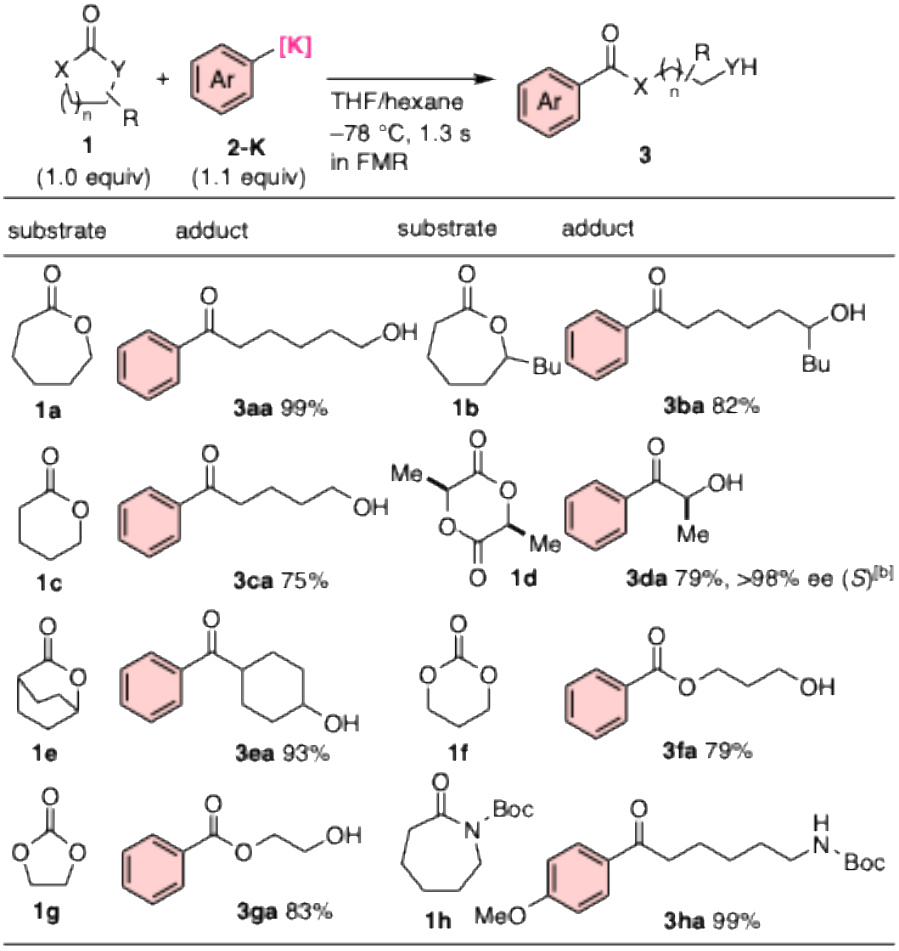
The optimized selective monoaddition system was applied to various cyclic carbonyl compounds (Table 4). Lactones with substituents at the *ε*-position are expected to exhibit different basicities of the alkoxide of the ring-opened compound; however, in this reaction system, the addition-ring-opening reaction proceeded smoothly, yielding product **3ba** in high yield. In the reaction with the six-membered δ-valerolactone **1c**, the corresponding product **3ca** was obtained in 75% yield with acceptable selectivity. Lactides used in ring-opening polymerization contain chiral carbon atoms, but through selective monoaddition–ring-opening reaction followed by hydrolysis, the corresponding chiral α-hydroxyketones **3da** were obtained in good yields while maintaining the enantiomeric excess. In the bicyclic lactone **1e**, despite its restricted conformation, ring-opening proceeded selectively, yielding the monoaddition product **3ea** in 93% yield. Furthermore, using cyclic carbonates with five- or six-membered rings, such as the cyclic carbonates **1f** and **1g**, the corresponding ω-hydroxy esters were synthesized in 83% and 79% yields, respectively. When using lactones with an alkyl group at the ε-position, the monohydroxy adduct of the secondary alcohol was selectively obtained in 82% yield. In the reaction of the seven-membered lactam **1h**, where the *N*-position was protected with a Boc group, with *p*-anisylpotassium species, the amide bond selectively cleaved, yielding the ring-opened compound ω-amidoketone **3ha** in nearly quantitative yield.

**Table 3**. Scope of various aromatic substituents for arylpotassium reagents.




[a] GC yield calibrated based on the isolated product.

**Table 4**. Scope of various lactones and lactams for flow arylpotassium monoaddition reactions.

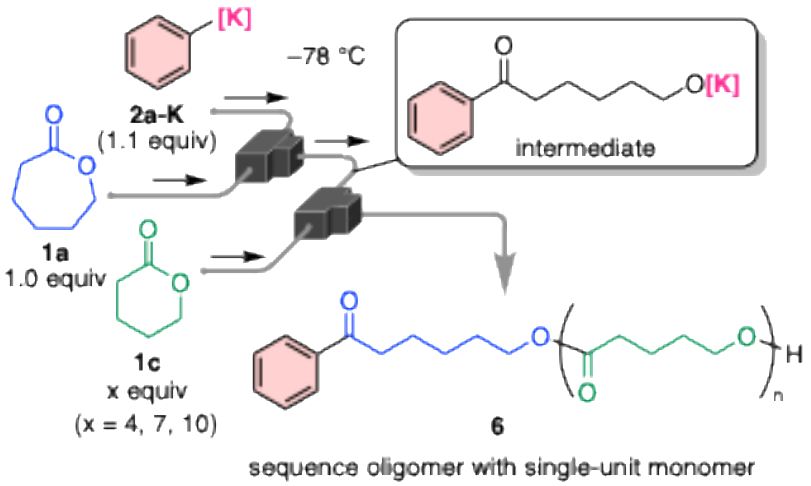



[a] Yields were determined by 1H NMR analysis using an internal standard (1,1,2,2-tetrachloroethane). [b] Determined with chiral HPLC analyses using Daicel Chiralpak IB column with eluent hexane/$^{i}$PrOH (v/v = 90/10).

This reaction system is an extremely fast reaction occurring in a micro-reaction space, so the author expected that controlled polymerization following kinetic behavior would occur through rapid mixing.[15,16] The author conducted the following model experiments aimed at realizing living anionic ring-opening polymerization with controlled sequences of two different lactones (Scheme 3). First, it was found that polymerization using a single monomer could be efficiently achieved by reacting the phenylpotassium species generated in the previous system with 10 equivalents of δ-valerolactone (**1c**) under flow conditions of −78 °C and 1.2 seconds (see Supporting Information). Next, alkoxide intermediates were generated through monoaddition using phenylpotassium species and ε-caprolactone (**1a**), followed by the addition of lactone monomer **1c** in different equivalents (4.0, 7.0, and 10 equiv.) to synthesize sequence oligomers

with various chain lengths. Analysis of the obtained oligomers by GPC revealed that all oligomers exhibited a uniform distribution of chain lengths, with molecular weight increasing monotonically as the equivalent of the lactone monomer increased. These results suggest that the organopotassium species at the growing end can selectively add lactone monomers with high selectivity and controllability while maintaining living properties, thereby indicating the potential for further synthesis of sequence oligomers. In the present hypothesis, the author assumes that the use of organopotassium mixed aggregates could enhance the ring-opening process into open-chain form, thus leading to the faster further oligomerization compared to the undesired over-addition of aryl nucleophiles (Scheme 1).

**Scheme 3**. Sequential arylpotassium monoaddition–oligomerization with two different lactone monomers using a flash flow system.



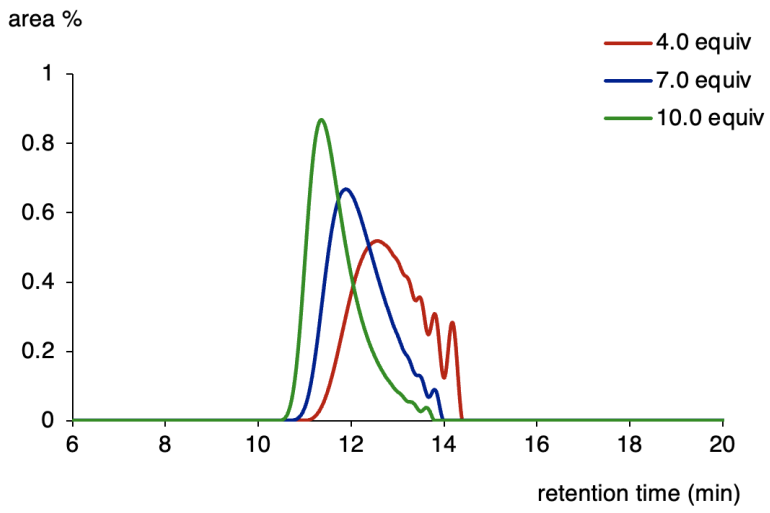



**Figure 1.** Gel permeation chromatograms for sequence oligomers **6** derived from the flow synthetic experiment using different equivalents of monomers (4.0, 7.0, and 10.0 equiv.). See supporting information for measurement conditions. Vertical axis means the area percentage ratio of RI intensities per 0.01 min. For x = 10, $M_n$ = 3.6 x $10^3$, $M_w/M_n$ = 1.31.

## 4-3. Conclusion

In conclusion, the author achieved selective monoaddition reactions of flash-generated organopotassium reagents to polymerizable lactones by designing a fast anionic flow control system. The results indicate that the reaction system is characterized by the ability to carry out monoaddition-selective ring-opening reactions without being affected by substrate structures such as ring strain or the presence of α-protons. The optimized flow system provides enough fast reactions to expand into oligomerization reactions with multiple equivalents of lactones as monomer. The sequential monoaddition–oligomerization afforded the polyester product with insertion of a single-monomer unit,[17] which demonstrates the synthetic utility of the present fast reaction system. The combination of reactive organopotassium aggregates and flash-flow control will deliver a general platform for precise synthesis of both functionalized ω-hydroxyketones and sequence oligolactones, advancing sustainable polyester production.

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## 4-5. Experimental Section

### 4-5-1. General

$^{1}H$ and $^{13}C$ NMR spectra were recorded in on JEOL ECZ-400S spectrometer ($^{1}H$ 400 MHz, $^{13}C$ 100 MHz). Chemical shifts are recorded using TMS (0.0 ppm) signals as an internal standard for $^{1}H$ NMR, and methine signal of $CHCl_3$ for $^{13}C$ NMR (77.0 ppm) unless otherwise noted. NMR yields were calculated by $^{1}H$ NMR analyses using TCE as an internal standard. GC analyses were performed on a SHIMADZU GC-2025 gas chromatograph equipped with a flame ionization detector using a fused silica capillary column (column, Rtx-200; 0.25 mm × 30 m). GC yields were calculated by GC analyses with *n*-tetradecane as an internal standard using calibration lines derived from commercial or isolated compounds with the internal standards. GC-MS analysis was performed on a SHIMADZU GCMS-QP2020 NX. GPC analysis was performed on a SHIMADZU CTO-20A with a Shodex RI-504 RI detector. Mass spectra were recorded on Thermo Fisher Scientific EXACTIVE plus (ESI and APCI) and JEOL JMS-700 (EI) in Instrumental Analysis Div., Global Facility Center, Creative Research Institution, Hokkaido University. Merck pre-coated silica gel $F_{254}$ plates (thickness 0.25 mm) were used for TLC analyses. Preparative GPC separation was performed on a JAI HPLC 9021 equipped with JAIGEL-1H and -2H columns. JASCO HPLC Gradient System (UV detector: UV-2075 Plus, plunger pump: PU-2089 Plus) was used for chiral HPLC analyses. All batch reactions were carried out in a flame-dried glassware under argon atmosphere unless otherwise noted.

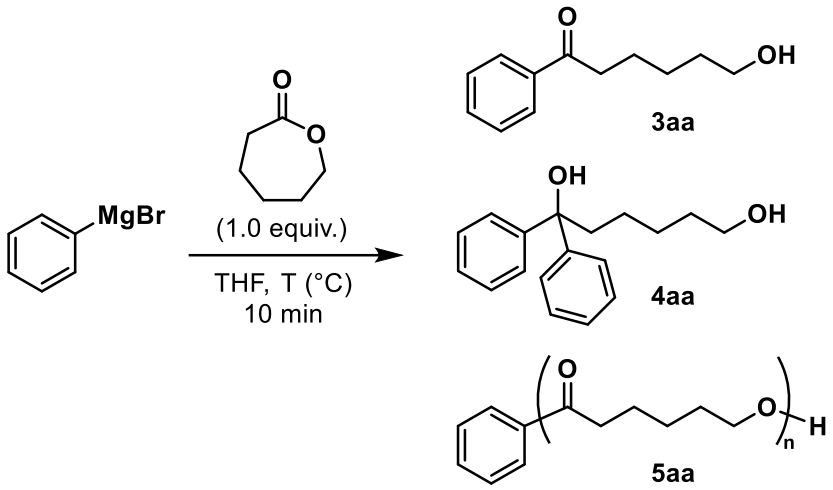
**Flow synthesis.** Stainless steel (SUS304) T-shaped micromixers with inner diameter of 500 μm and 250 μm were manufactured by Sanko Seiki Co., Inc. Stainless steel (SUS316) microtube reactors with 1000 μm inner diameter and PTFE tubes with inner diameter of 1000 μm were purchased from GL Sciences. The syringe pumps (Harvard PHD ULTRA) equipped with gastight syringes (SGE 50MR-LL-GT or 100MR-LL-GT) were used for introduction of the solutions into the micromixer systems *via* stainless steel fittings (GL Sciences, 1/16 OUW). Flow microreactor system is composed with stainless steel pre-cooling units (**P1**, **P2**, etc.), stainless steel microtube reactors (**R1**, **R2**, etc.), T-shaped micromixers (**M1**, **M2**, etc.), and, if necessary, PTFE tube with inner diameter of 1000 μm. The solution of *n*-butyllithium and *sec*-butyllithium was prepared by dilution of those commercial solution with dehydrated *n*-hexane.

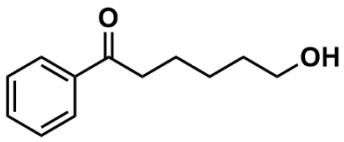
**Materials.** Dry THF and *n*-hexane were purchased from Kanto Chemical and were used after passing through the purification column in the solvent dispenser system. Solutions of *n*-butyllithium ($^{n}$BuLi) and potassium *tert*-butoxide (KO$^{t}$Bu) were purchased from Kanto Chemical and Sigma-Aldrich (Merck) and stored at 0 °C. Aryl bromides were purchased from commercial

suppliers.

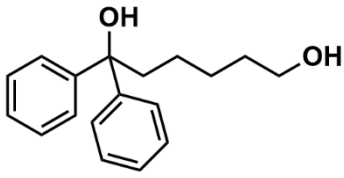
### 4-5-2. Effect of temperature on ring-opening monoaddition of arylmetal reagents in a batch-type reactor.

#### 4-5-2-1. PhMgBr

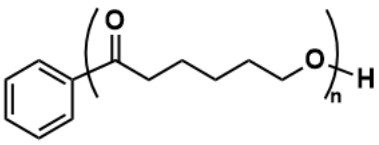


**6-hydroxy-1-phenylhexan-1-one (3aa):** The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 7.6 Hz, 2H), 7.55 (t, *J* = 7.2 Hz, 1H), 7.45 (t, *J* = 7.6 Hz, 2H), 3.67 (t, *J* = 6.4 Hz, 2H), 2.99 (t, *J* = 7.6 Hz, 2H), 1.77 (quin, *J* = 7.6 Hz, 2H), 1.59-1.66 (m, 2H), 1.42-1.49 (m, 2H), 1.36 (broad, 1H); $^{13}C$ NMR (100MHz, $CDCl_3$) δ 200.8, 137.0, 133.1, 128.7 (2C), 128.1 (2C), 62.5, 38.5, 32.5, 25.5, 24.0. HRMS (ESI) *m/z* Calcd for $C_{12}H_{16}O_2Na$ $[M+Na]^+$ 215.1043; Found: 215.1039.



**1,1-diphenylhexane-1,6-diol (4aa):** The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.42-7.39 (m, 4H), 7.33-7.29 (m, 4H), 7.24-7.20 (m, 2H), 3.59 (t, *J* = 6.8 Hz, 2H), 2.31-2.27 (m, 2H), 2.27-2.02 (broad, 1H), 1.71-1.13 (m, 7H); $^{13}C$ NMR (100MHz, $CDCl_3$) δ 200.8, 147.0 (2C), 128.1 (4C), 126.8 (2C), 126.0 (4C), 78.2, 62.9, 41.8, 32.5, 26.1, 23.5. HRMS (ESI) *m/z* Calcd for $C_{18}H_{22}O_2Na$ $[M+Na]^+$ 293.1512; Found: 293.1507.



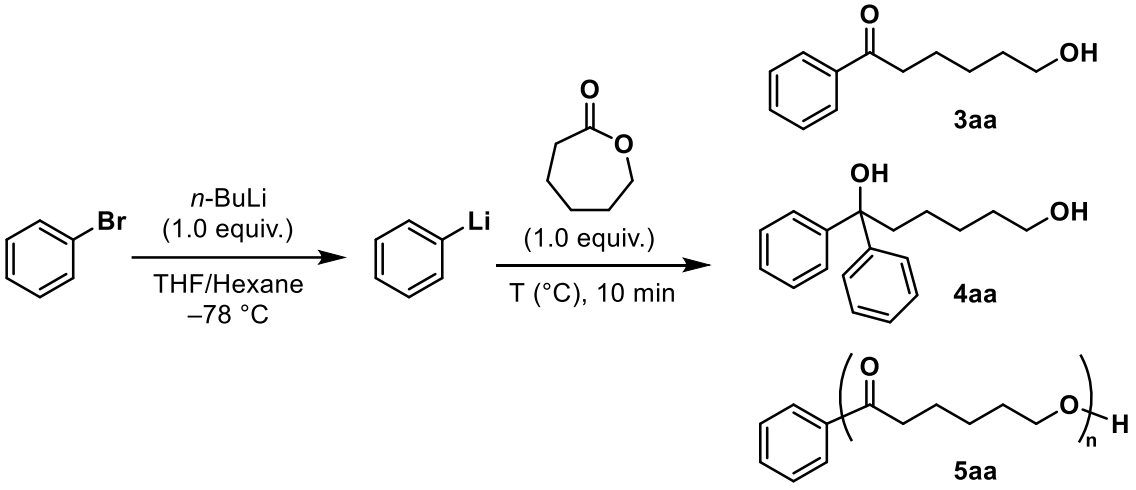
**Oligomer 5aa:** The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$) δ 7.97-7.94 (m, 2H), 7.58-7.52 (m, 1H), 7.49-7.43 (m, 2H), 4.18-4.01 (m, 38H), 3.66-3.63 (m, 2H), 3.03-2.96 (m, 2H), 2.39-2.24 (m, 35H), 1.82-1.55 (m, 74H), 1.51-1.35 (m, 37H).

To solution of phenyl magnesium bromide (0.4 M in THF, 1 mL (0.4 mmol)), ε-caprolactone (0.2 M in THF, 2 mL (0.4 mmol)) was added dropwise at *T* (°C) and stirred for 10 min at this temperature, and then quenched with $NH_4Cl$ aq. (3 mL) at this temperature. The crude mixture was evaporated in vacuum and yields were determined by $^1$H NMR analysis using an internal standard (1,1,2,2-tetrachloroethane).

**Table 5.** Investigations for anionic ring opening monoaddition of temperature with phenyl magnesium bromide in macro-batch reactor.

| entry | *T* (°C) | **1a** conversion (%) | NMR yield (%) | | |
|---|---|---|---|---|---|
| | | | **3aa** | **4aa** | **5aa** (oligomer) |
| 1 | 0 | 96 | 64 | 19 | 16 |
| 2 | –78 | 30 | 5 | 2 | 3 |

**4-5-2-2. PhLi**



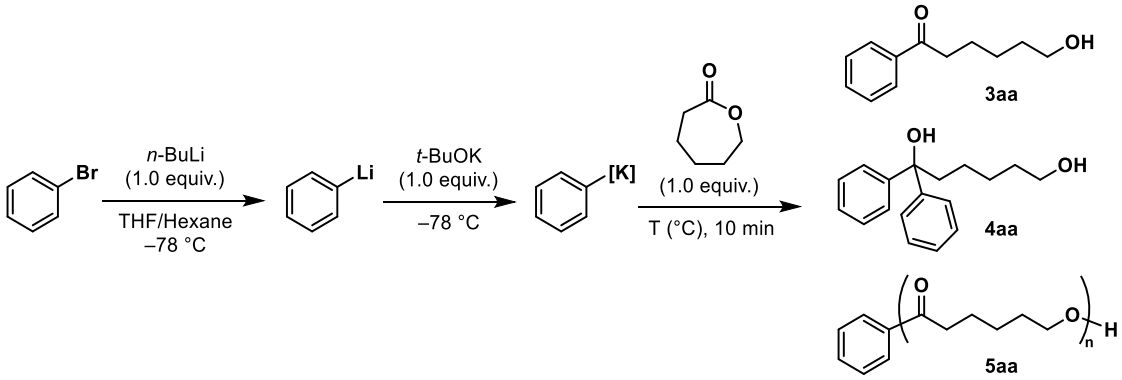

To solution of phenyl bromide (0.20 M in THF, 2.0 mL (0.40 mmol)), $^n$BuLi (0.40 M in THF, 1.0 mL (0.40 mmol)) was added dropwise at –78 °C and stirred for 60 min at this temperature, and ε-caprolactone (0.20 M in THF, 2.0 mL (0.40 mmol)) was added dropwise at *T* °C and stirred for 10 min at this temperature, and then quenched with $NH_4Cl$ aq. (ca. 3 mL) at this temperature. The crude mixture was evaporated in vacuum and yields were determined by $^1$H NMR analysis

using an internal standard (1,1,2,2-tetrachloroethane).

**Table 6.** Investigations for anionic ring opening monoaddition of temperature with phenyl lithium in macro-batch reactor.

| entry | *T* (°C) | **1a** conversion (%) | NMR yield (%) | | |
|---|---|---|---|---|---|
| | | | **3aa** | **4aa** | **5aa** (oligomer) |
| 1 | 0 | 98 | 5 | 31 | 62 |
| 2 | –78 | 79 | 34 | 27 | 6 |

#### 4-5-2-3. Ph[K] (PhLi + KO$^t$Bu)



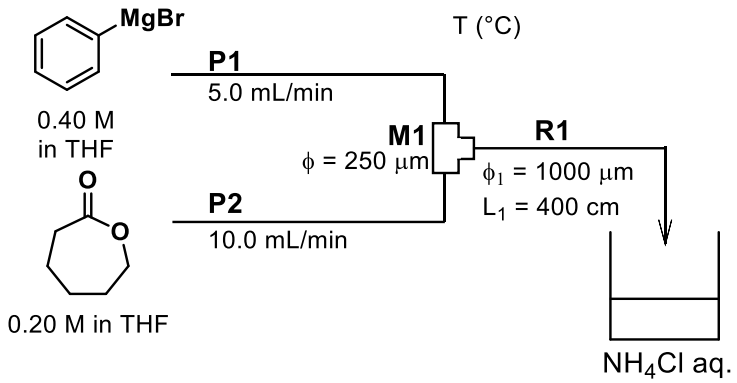

To solution of phenyl bromide (0.20 M in THF, 2.0 mL (0.40 mmol)), $^n$BuLi (0.40 M in THF, 1 mL (0.40 mmol)) was added dropwise at –78 °C and stirred for 60 min at this temperature, and then KO$^t$Bu (0.40 M in THF, 1.0 mL (0.40 mmol)) and *ε*-caprolactone (0.20 M in THF, 2.0 mL (0.40 mmol)) was added dropwise sequentially at *T* °C and stirred for 10 min at this temperature, and then quenched with $NH_4Cl$ aq. (ca. 3 mL) at this temperature. The crude mixture was evaporated in vacuum and yields were determined by $^1$H NMR analysis using an internal standard (1,1,2,2-tetrachloroethane).

**Table 7.** Investigations for anionic ring opening monoaddition of temperature with phenyl potassium in macro-batch reactor.

| entry | *T* | **1a** conversion (%) | NMR yield (%) | | |
|---|---|---|---|---|---|
| | (°C) | | **3aa** | **4aa** | **5aa** (oligomer) |
| 1 | 0 | 99 | 12 | 64 | 27 |
| 2 | –78 | 96 | 37 | 44 | 6 |

### 4-5-3. Effect of temperature on ring-opening monoaddition of arylmetal reagents in a flow microreactor.

#### 4-5-3-1. PhMgBr




A flow microreactor system consisting of T-shaped micromixer (**M1**), microtube reactor (**R1**), and two pre-cooling units was used in a cooling bath at *T* (°C) (**P1** (L = 100 cm) and **P2** (100 cm)). A solution of phenyl magnesium bromide (0.40 M in THF, flow rate: 5.0 mL/min) and a solution of ε-caprolactone (0.20 M in THF, flow rate: 10.0 mL/min) were introduced to **M1** ($\phi$ = 250 μm) using syringe pumps, and the mixture was passed through **R1** ($\phi$ = 1000 μm, 400 cm, residence time $t^{R1}$ = 12.6 s). After a steady state was reached, the product solution was collected for 30 seconds. To the aliquot, sat. $NH_4Cl$ aq. was added, and then the organic phase was analyzed by NMR.

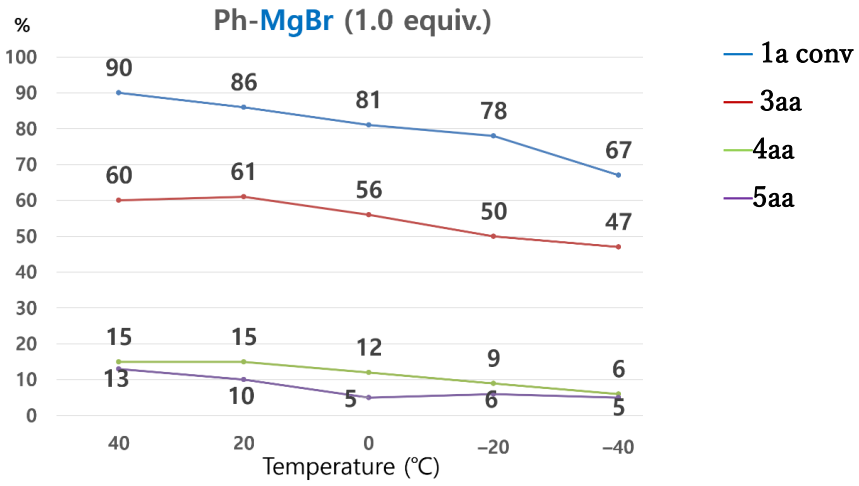
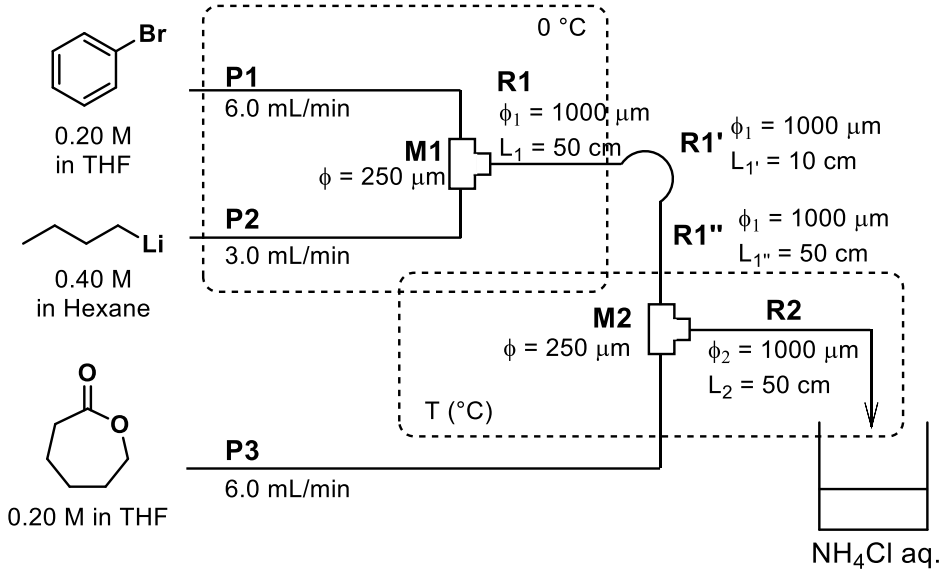



**Figure 2.** Results of anionic ring opening monoaddition of phenyl magnesium bromide on temperature in flow microreactor.

**4-5-3-2. PhLi**




A flow microreactor system consisting of two T-shaped micromixers (**M1**, **M2**), four microtube reactors (**R1**, **R1'**, **R1"** and **R2**), and three pre-cooling units was used in a cooling bath at 0 °C (**P1** (L = 100 cm) and **P2** (50 cm)) and –78 °C (**P3** (50 cm)). A solution of phenyl bromide (0.20 M in THF, flow rate: 6.0 mL/min) and a solution of *n*-BuLi (0.40 M in hexane, flow rate: 3.0 mL/min) were introduced to **M1** ($\phi$ = 250 μm) using syringe pumps, and the mixture was passed through **R1** ($\phi$ = 1000 μm, 50 cm, residence time $t^{R1}$ = 2.4 s), **R1'** ($\phi$ = 1000 μm, 10 cm, residence time $t^{R1'}$ = 0.5 s) and **R1"** ($\phi$ = 1000 μm, 50 cm, residence time $t^{R1"}$ = 2.4 s). The resulting solution was introduced to **M2** ($\phi$ = 250 μm), where a solution of ε-caprolactone (0.20 M in THF) was also introduced (flow rate: 6.0 mL/min). The resulting solution was passed through **R2** ($\phi$ = 1000 μm, L = 50 cm, residence time = 1.6 s). After a steady state was reached, the product solution was collected for 30 seconds. To the aliquot, sat. $NH_4Cl$ aq. was added, and then the organic phase was analyzed by NMR.

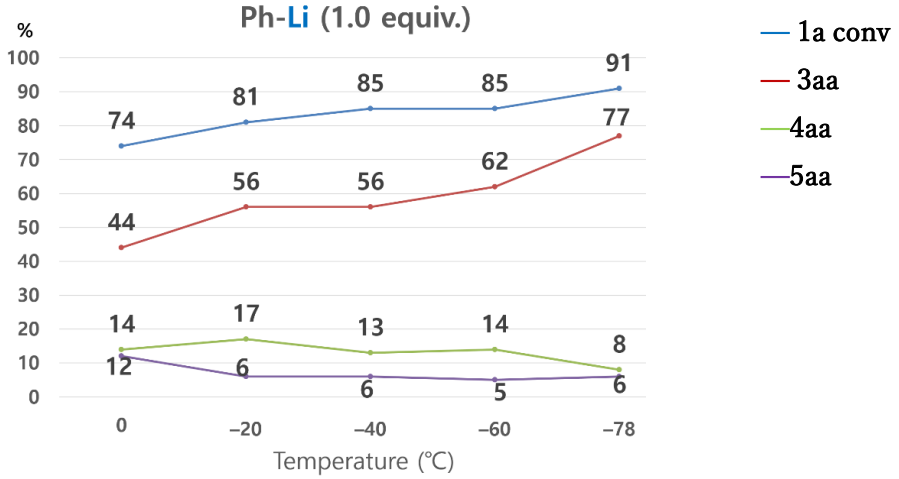
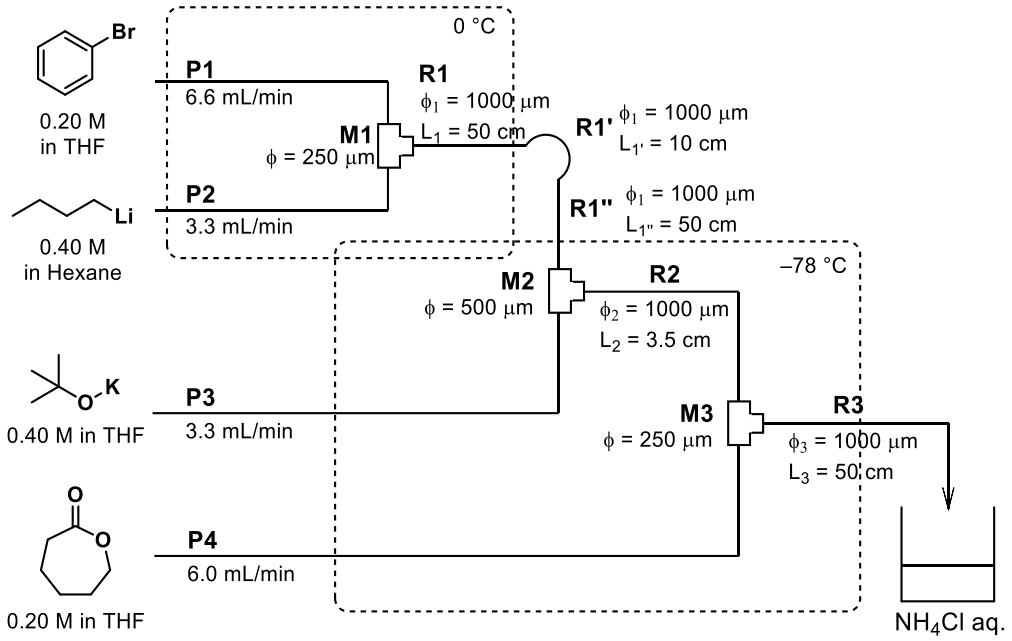



**Figure 3.** Results of anionic ring opening monoaddition of phenyl lithium on temperature in flow

microreactor.

### 4-5-3-3. Ph[K] (PhLi + KO$^t$Bu)




A flow microreactor system consisting of three T-shaped micromixers (**M1**, **M2** and **M3**), five microtube reactors (**R1**, **R1'**, **R1"**, **R2** and **R3**), and four pre-cooling units was used in a cooling bath at 0 °C (**P1** (L = 100 cm) and **P2** (50 cm)) and –78 °C (**P3** (50 cm) and **P4** (100 cm)). A solution of phenyl bromide (0.20 M in THF, flow rate: 6.0 mL/min) and a solution of *n*-BuLi (0.40 M in hexane, flow rate: 3.0 mL/min) were introduced to **M1** ($\phi$ = 250 μm) using syringe pumps, and the mixture was passed through **R1** ($\phi$ = 1000 μm, 50 cm, residence time $t^{R1}$ = 2.4 s), **R1'** ($\phi$ = 1000 μm, 10 cm, residence time $t^{R1'}$ = 0.5 s) and **R1"** ($\phi$ = 1000 μm, 50 cm, residence time $t^{R1"}$ = 2.4 s). The resulting solution was introduced to **M2** ($\phi$ = 500 μm), where a solution of *t*-BuOK (0.40 M in THF) was also introduced (flow rate: 3.0 mL/min). The resulting solution was passed through **R2** ($\phi$ = 1000 μm, L = 3.5 cm, residence time = 0.1 s). The resulting solution was introduced to **M3** ($\phi$ = 250 μm), where a solution of ε-caprolactone (0.20 M in THF) was also introduced (flow rate: 6.0 mL/min). The resulting solution was passed through **R3** ($\phi$ = 1000 μm, L = 50 cm, residence time = 1.2 s). After a steady state was reached, the product solution was collected for 30 seconds. To the aliquot, sat. $NH_4Cl$ aq. was added, and then the organic phase was analyzed by NMR.

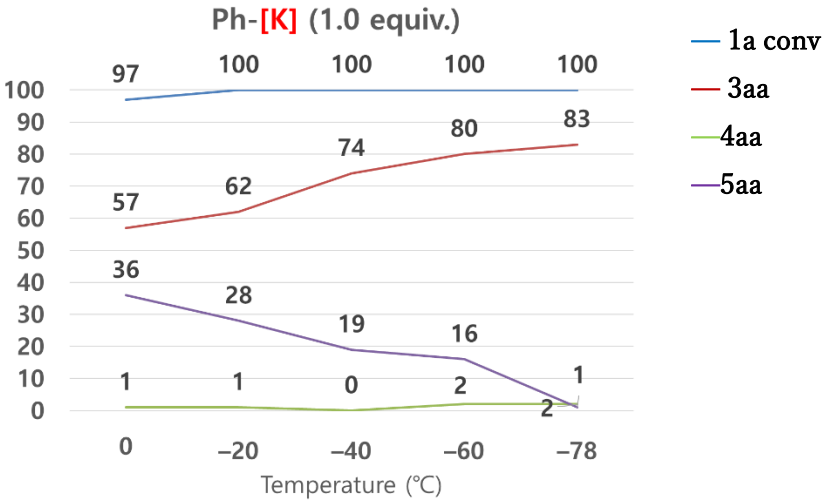



**Figure 4.** Results of anionic ring opening monoaddition of phenyl potassium on temperature in flow microreactor.

### 4-5-4. Effect of residence time on ring-opening monoaddition of Ph[K] with ε-caprolactone in the flow microreactor.

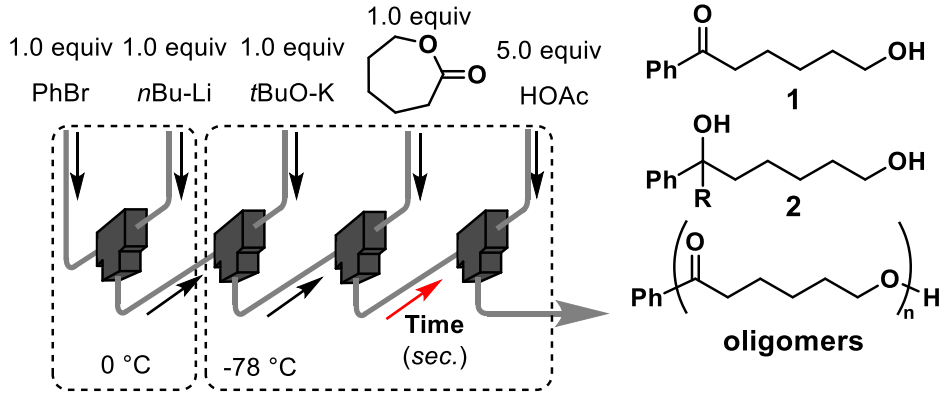



**Table 8.** Investigations for anionic ring opening monoaddition of retention time in flow microreactor.

| *t* (s) | **1a** conversion (%) | GC yield (%) | | |
|---|---|---|---|---|
| | | **3aa** | **4aa** | **5aa** (oligomer) |
| 0.09 | 84 | 62 | 0 | 0 |
| 0.13 | 97 | 78 | 2 | 0 |
| 0.33 | 96 | 82 | 2 | 0 |
| 0.65 | 96 | 80 | 2 | 1 |
| 1.31 | 98 | 82 | 2 | 2 |
| 2.62 | 98 | 81 | 2 | 1 |
| 5.24 | 100 | 83 | 3 | 0 |

### 4-5-5. Effect of mixing on ring-opening monoaddition of Ph[K] with ε-caprolactone in the flow microreactor.

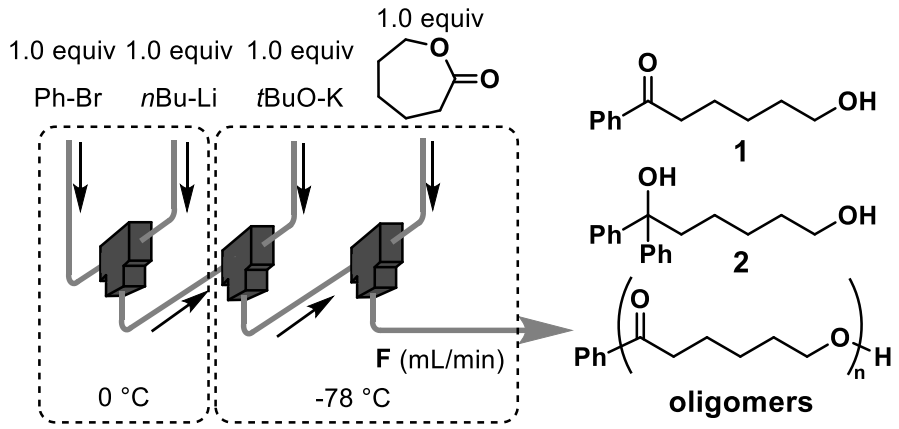



**Table 9.** Investigations for anionic ring opening monoaddition of flow rate in flow microreactor.

| entry | *F* (mL/min) | **1a** conversion (%) | NMR yield (%) | | |
|---|---|---|---|---|---|
| | | | **3aa** | **4aa** | **5aa** (oligomer) |
| 1 | 6 | 99 | 41 | 15 | 33 |
| 2 | 12 | 100 | 64 | 12 | 18 |
| 3 | 18 | 100 | 83 | 3 | 0 |

### 4-5-6. Effect of organometallic equivalent on ring-opening monoaddition of ε-caprolactone in the flow microreactor.

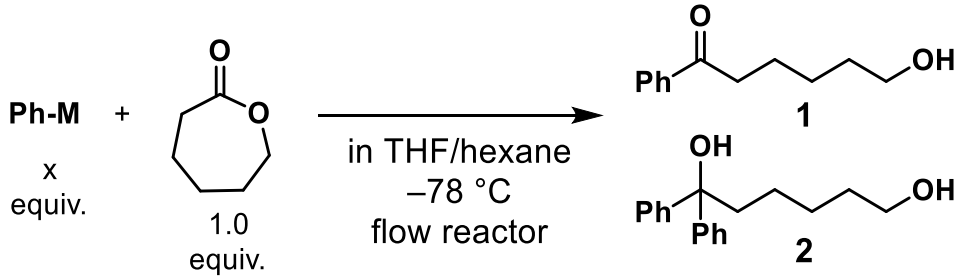
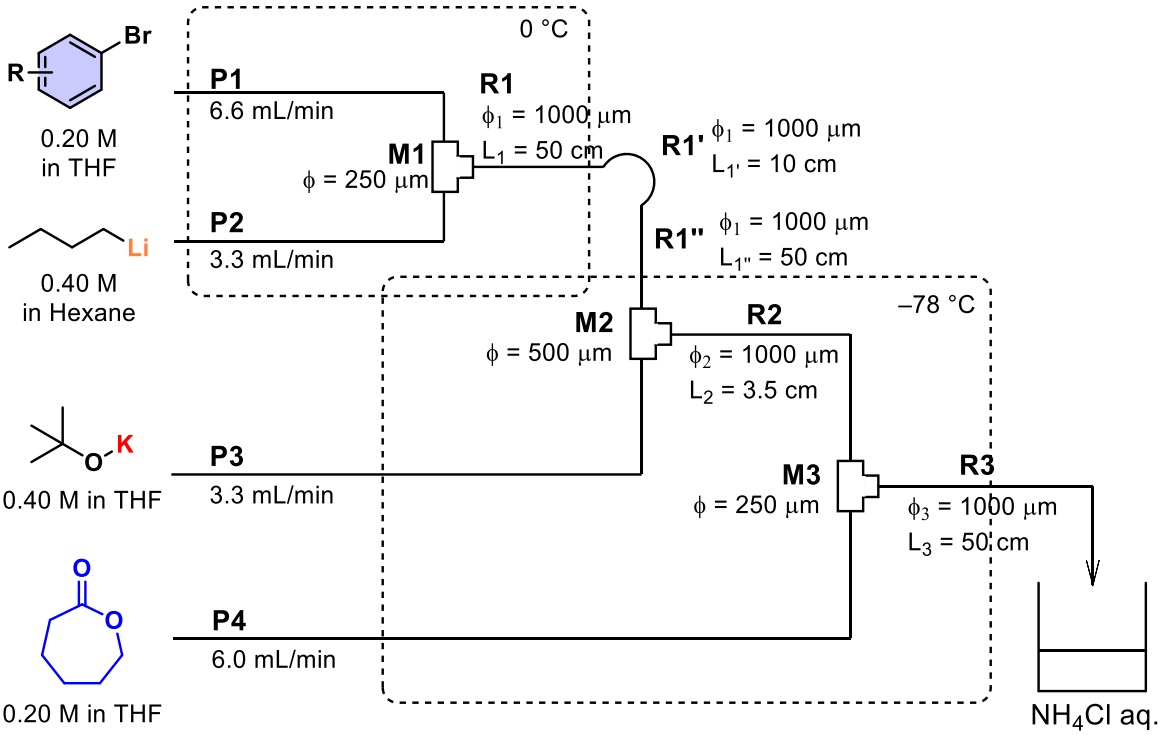



**Table 10.** Investigations for anionic ring opening monoaddition on equivalent of phenyl metal in flow microreactor.

| entry | Ph-M | x (equiv) | **1a** conversion (%) | NMR yield (%) | | |
|---|---|---|---|---|---|---|
| | | | | **3aa** | **4aa** | **5aa** (oligomer) |
| 1 | Ph-Li | 1.0 | 91 | 77 | 8 | 6 |
| 2 | | 1.1 | 96 | 65 | 19 | 4 |

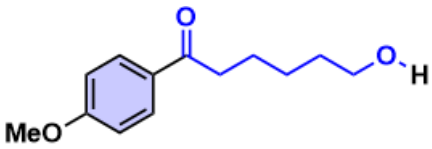
| | | | | | | |
|---|---|---|---|---|---|---|
| 3 | | 1.5 | 100 | 48 | 40 | 3 |
| 4 | | 2.0 | 100 | 32 | 71 | 0 |
| 5 | | 3.0 | 100 | 25 | 76 | 0 |
| 6 | Ph-[K] | 1.0 | 100 | 79 | 3 | 9 |
| 7 | | 1.1 | 100 | 99 | 1 | 0 |
| 8 | | 1.5 | 100 | 86 | 14 | 0 |
| 9 | | 2.0 | 100 | 74 | 27 | 0 |
| 10 | | 3.0 | 100 | 68 | 33 | 0 |

**4-5-7. Synthesis of monoaddition product via arylpotassium reagents in a flow microreactor.**

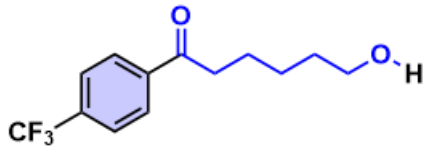



A flow microreactor system consisting of three T-shaped micromixers (**M1**, **M2** and **M3**), five microtube reactors (**R1**, **R1'**, **R1"**, **R2** and **R3**), and four pre-cooling units was used in a cooling bath at 0 °C (**P1** (L = 100 cm) and **P2** (50 cm)) and –78 °C (**P3** (50 cm) and **P4** (100 cm)). A solution of aryl bromide (0.20 M in THF, flow rate: 6.6 mL/min) and a solution of $^{n}$BuLi (0.40 M in hexane, flow rate: 3.3 mL/min) were introduced to **M1** ($\phi$ = 250 μm) using syringe pumps, and the mixture was passed through **R1** ($\phi$ = 1000 μm, 50 cm, residence time $t^{R1}$ = 2.4 s), **R1'** ($\phi$ = 1000 μm, 10 cm, residence time $t^{R1'}$ = 0.5 s) and **R1"** ($\phi$ = 1000 μm, 50 cm, residence time $t^{R1"}$ = 2.4 s). The resulting solution was introduced to **M2** ($\phi$ = 500 μm), where a solution of *t*-BuOK (0.40 M in THF) was also introduced (flow rate: 3.3 mL/min). The resulting solution was passed

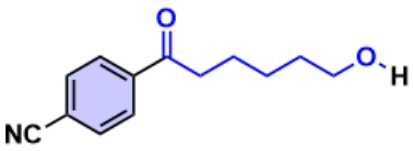
through **R2** ($\phi$ = 1000 μm, L = 3.5 cm, residence time = 0.1 s). The resulting solution was introduced to **M3** ($\phi$ = 250 μm), where a solution of $\varepsilon$-caprolactone (0.20 M in THF) was also introduced (flow rate: 6.0 mL/min). The resulting solution was passed through **R3** ($\phi$ = 1000 μm, L = 50 cm, residence time = 1.2 s). After a steady state was reached, the product solution was collected for 30 seconds. To the aliquot, sat. $NH_4Cl$ aq. was added, and then the organic phase was analyzed by GC and NMR.




**6-hydroxy-1-(4-methoxyphenyl)hexan-1-one (3ab) :** Obtained from 1-bromo-4-methoxybenzene as the aryl bromide in 98% yield (GC yield). Yields were determined by GC analysis using an internal standard ($C_{14}H_{30}$). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 83% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, $J$ = 1.6 Hz, 2H), 7.85 (t, $J$ = 1.6 Hz, 1H), 3.68 (t, $J$ = 6.4 Hz, 2H), 2.94 (t, $J$ = 7.2 Hz, 2H), 1.77 (quin, $J$ = 8.0 Hz, 2H), 1.67-1.60 (m, 3H), 1.50-1.42 (m, 2H); $^{13}$C NMR (100MHz, $CDCl_3$) δ 199.1, 163.2, 130.2 (2C), 129.8, 113.5 (2C), 62.3, 55.3, 38.0, 32.3, 25.3, 24.0. HRMS (ESI) *m/z* Calcd for $C_{12}H_{18}O_3Na$ $[M+Na]^+$ 245.1148; Found: 245.1140.

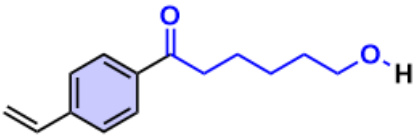



**6-hydroxy-1-(4-(trifluoromethyl)phenyl)hexan-1-one (3ac) :** Obtained from 1-bromo-4-(trifluoromethyl)benzene as the aryl bromide in 96% yield (GC yield). Yields were determined by GC analysis using an internal standard ($C_{14}H_{30}$). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 71% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, $J$ = 7.6 Hz, 2H), 7.72 (d, $J$ = 8.4 Hz, 2H), 3.67 (t, $J$ = 6.0 Hz, 2H), 3.01 (t, $J$ = 7.6 Hz, 2H), 1.78 (quin, $J$ = 7.2 Hz, 2H), 1.66-1.59 (m, 2H), 1.50-1.42 (m, 2H), 1.30 (broad, 1H); $^{13}$C NMR (100MHz, $CDCl_3$) δ 199.6, 139.6, 134.2, 128.4 (2C), 125.7 (2C), 123.6, 62.3, 38.8, 32.4, 25.4, 23.7. HRMS (ESI) *m/z* Calcd for $C_{13}H_{15}O_2F_3Na$ $[M+Na]^+$ 283.0916; Found: 283.0910.

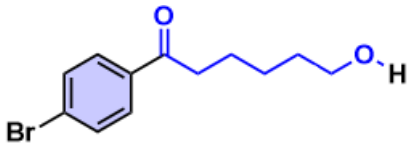



**4-(6-hydroxyhexanoyl)benzonitrile (3ad) :** Obtained from 4-bromobenzonitrile as the aryl bromide in 94% yield (GC yield). Yields were determined by GC analysis using an internal standard ($C_{14}H_{30}$). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 72% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.99 (d, $J$ = 8.5 Hz, 2H), 7.72 (d, $J$ = 8.8 Hz, 2H), 3.60 (t, $J$ = 6.4 Hz, 2H), 2.96 (t, $J$ = 7.2 Hz, 2H), 2.39 (broad, 1H), 1.72 (quin, $J$ = 7.2 Hz, 2H), 1.60-1.53 (m, 2H), 1.45-1.37 (m, 2H); $^{13}$C NMR (100MHz, $CDCl_3$) δ 199.2, 139.9, 132.6 (2C), 128.5 (2C),

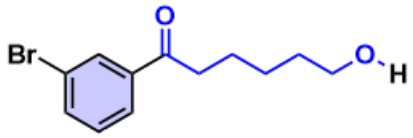
118.1, 116.2, 62.4, 38.8, 32.4, 25.4, 23.7. HRMS (ESI) *m/z* Calcd for $C_{13}H_{15}O_2NNa$ $[M+Na]^+$ 240.0995; Found: 240.0989.



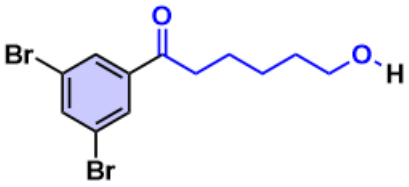
**6-hydroxy-1-(4-vinylphenyl)hexan-1-one (3af) :** Obtained from 1-bromo-4-vinylbenzene as the aryl bromide in 99% yield (GC yield). Yields were determined by GC analysis using an internal standard ($C_{14}H_{30}$). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 78% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.93 (d, *J* = 8.4 Hz, 2H),7.49 (d, *J* = 8.0 Hz, 2H), 6.76 (dd, *J* = 18.0, 10.8 Hz, 1H), 5.88 (d, *J* = 17.6 Hz, 1H), 5.40 (d, *J* = 11.2 Hz, 1H), 3.68 (t, *J* = 6.4 Hz, 2H), 2.99 (t, *J* = 7.2 Hz, 2H), 1.78 (quin, *J* = 7.6 Hz, 2H), 1.67-1.43 (m, 5H); $^{13}$C NMR (100MHz, $CDCl_3$) δ 197.5, 139.5, 137.9 (2C), 129.7 (4C), 123.3, 62.3, 38.4, 32.2, 25.2, 23.4. HRMS (ESI) *m/z* Calcd for $C_{14}H_{18}O_2Na$ $[M+Na]^+$ 241.1199; Found: 241.1194.



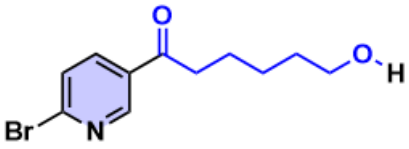
**1-(4-bromophenyl)-6-hydroxyhexan-1-one (3ag) :** Obtained from 1,4-dibromobenzene as the aryl bromide in 94% yield (GC yield). Yields were determined by GC analysis using an internal standard ($C_{14}H_{30}$). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 75% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 7.6 Hz, 2H), 7.59 (d, *J* = 7.6 Hz, 2H), 3.66 (t, *J* = 6.8 Hz, 3H), 2.95 (t, *J* = 6.8 Hz, 2H), 2.24-1.93 (broad, 1H), 1.76 (quin, *J* = 8.0 Hz, 2H), 1.62 (quin, *J* = 7.2 Hz, 2H), 1.49-1.41 (m, 2H); $^{13}$C NMR (100MHz, $CDCl_3$) δ 199.3, 153.5, 131.8 (2C), 129.5 (2C), 128.0, 62.4, 38.3, 32.3, 25.3, 23.7. HRMS (ESI) *m/z* Calcd for $C_{12}H_{15}O_2BrNa$ $[M+Na]^+$ 293.0148; Found: 293.0142.



**1-(3-bromophenyl)-6-hydroxyhexan-1-one (3ah) :** Obtained from 1,3-dibromobenzene as the aryl bromide in 97% yield (GC yield). Yields were determined by GC analysis using an internal standard ($C_{14}H_{30}$). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 85% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.08-8.07 (m, 1H), 7.88-7.86 (m, 1H), 7.70-7.68 (m, 1H), 7.36-7.32 (m, 1H), 3.68 (t, *J* = 6.4 Hz, 2H), 2.96 (t, *J* = 7.2 Hz, 2H), 1.78 (quin, *J* = 7.2 Hz, 2H), 1.63 (quin, *J* = 6.4 Hz, 2H), 1.50-1.43 (m, 2H), 0.79 (broad, 1H); $^{13}$C NMR (100MHz, $CDCl_3$) δ 199.2, 138.6, 135.9, 131.1, 130.3, 126.7, 123.0, 62.4, 38.6, 32.5, 25.5, 23.8. HRMS (ESI) *m/z* Calcd for $C_{12}H_{15}O_2BrNa$ $[M+Na]^+$ 293.0148; Found: 293.0140

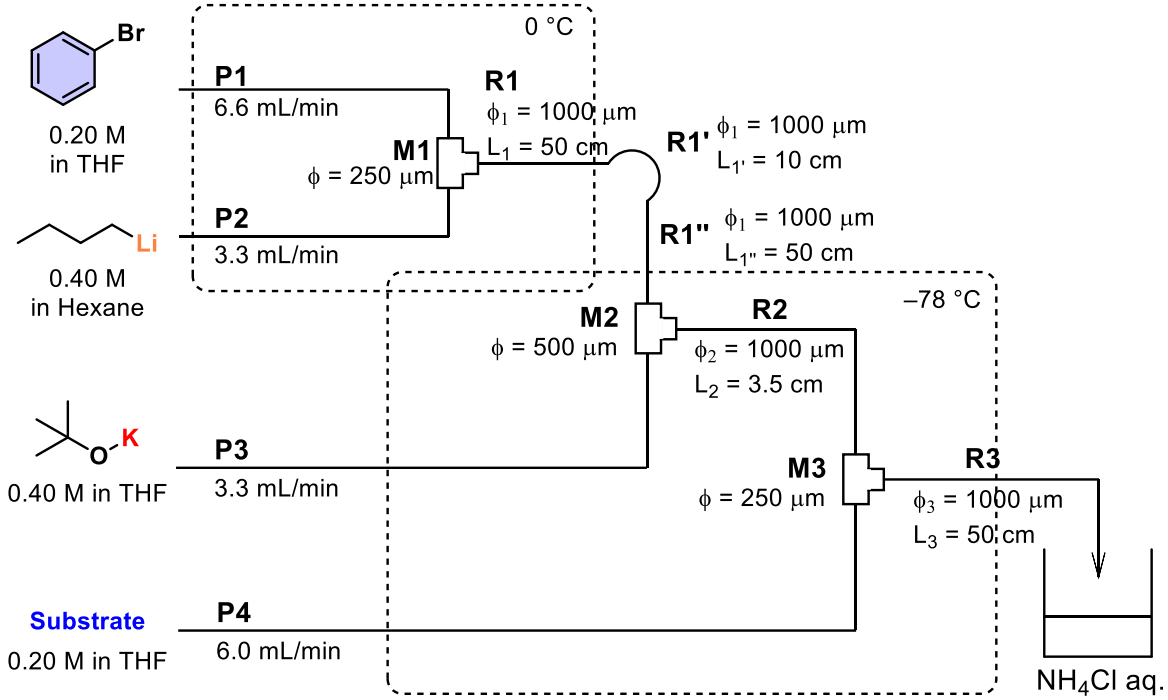



**1-(3,5-dibromophenyl)-6-hydroxyhexan-1-one (3ai) :** Obtained from 1,3,5-tribromobenzene as the aryl bromide in 91% yield (GC yield). Yields were determined by GC analysis using an internal standard ($C_{14}H_{30}$). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 77% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.00 (d, *J* = 1.6 Hz, 2H), 7.85 (t, *J* = 1.6 Hz, 1H), 3.68 (t, *J* = 6.4 Hz, 2H), 2.94 (t, *J* = 7.2 Hz, 2H), 1.77 (quin, *J* = 8.0 Hz, 2H), 1.67-1.60 (m, 3H), 1.50-1.42 (m, 2H); $^{13}$C NMR (100MHz, $CDCl_3$) δ 199.9, 141.9, 136.0, 135.8, 128.4, 126.2, 116.6, 62.5, 38.4, 32.4, 25.4, 23.9. HRMS (ESI) *m/z* Calcd for $C_{12}H_{14}O_2Br_2Na$ $[M+Na]^+$ 370.9253; Found: 370.9247.

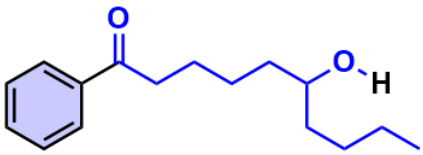



**1-(6-bromopyridin-3-yl)-6-hydroxyhexan-1-one (3aj) :** Obtained from 2,5-dibromopyridine as the aryl bromide in 97% yield (GC yield). Yields were determined by GC analysis using an internal standard ($C_{14}H_{30}$). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 79% isolated yield. $^1$H NMR (400 MHz, $CDCl_3$) δ 8.91 (d, *J* = 2.4 Hz, 1H), 8.08 (dd, *J* = 8.4, 2.4 Hz, 1H), 7.62 (d, *J* = 8.0 Hz, 1H), 3.69-3.67 (m, 2H), 2.99 (t, *J* = 7.2 Hz, 2H), 1.80 (quin, *J* = 8.0 Hz, 2H), 1.68-1.61 (m, 2H), 1.52-1.44 (m, 2H), 1.32 (broad, 1H); $^{13}$C NMR (100MHz, $CDCl_3$) δ 198.2, 150.1, 146.7, 137.7, 131.3, 128.5, 62.4, 38.9, 32.4, 25.4, 23.5. HRMS (ESI) *m/z* Calcd for $C_{11}H_{14}O_2NBrNa$ $[M+Na]^+$ 294.0100; Found: 294.0095.

**4-5-8. Synthesis of monoaddition product via substrate in a flow microreactor.**

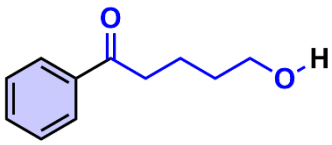



A flow microreactor system consisting of three T-shaped micromixers (**M1**, **M2** and **M3**), five microtube reactors (**R1**, **R1'**, **R1"**, **R2** and **R3**), and four pre-cooling units was used in a cooling bath at 0 °C (**P1** (L = 100 cm) and **P2** (50 cm)) and –78 °C (**P3** (50 cm) and **P4** (100 cm)). A solution of aryl bromide (0.20 M in THF, flow rate: 6.6 mL/min) and a solution of *n*-BuLi (0.40 M in hexane, flow rate: 3.3 mL/min) were introduced to **M1** ($\phi$ = 250 μm) using syringe pumps, and the mixture was passed through **R1** ($\phi$ = 1000 μm, 50 cm, residence time $t^{R1}$ = 2.4 s), **R1'** ($\phi$ = 1000 μm, 10 cm, residence time $t^{R1'}$ = 0.5 s) and **R1"** ($\phi$ = 1000 μm, 50 cm, residence time $t^{R1"}$ = 2.4 s). The resulting solution was introduced to **M2** ($\phi$ = 500 μm), where a solution of *t*-BuOK (0.40 M in THF) was also introduced (flow rate: 3.3 mL/min). The resulting solution was passed through **R2** ($\phi$ = 1000 μm, L = 3.5 cm, residence time = 0.1 s). The resulting solution was introduced to **M3** ($\phi$ = 250 μm), where a solution of substrate (0.20 M in THF) was also introduced (flow rate: 6.0 mL/min). The resulting solution was passed through **R3** ($\phi$ = 1000 μm, L = 50 cm, residence time = 1.2 s). After a steady state was reached, the product solution was collected for 30 seconds. To the aliquot, sat. $NH_4Cl$ aq. was added, and then the organic phase was analyzed by GC and NMR.

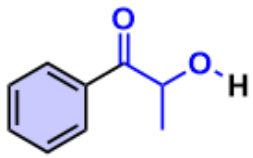



**6-hydroxy-1-phenyldecan-1-one (3ba):** Obtained from 7-butyloxepan-2-one as the substrate in 82% yield (NMR yield). Yields were determined by $^1$H NMR analysis using an internal standard (1,1,2,2-tetrachloroethane). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the

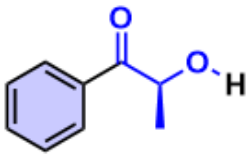
product in 64% isolated yield. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.95-7.92 (m, 2H), 7.57-7.50 (m, 1H), 7.45-7.40 (m, 2H), 3.60 (s, 1H), 2.99-2.94 (m, 2H), 1.77-1.29 (m, 13H), 0.90-0.86 (m, 3H). $^{13}$C NMR (100MHz, $CDCl_3$) δ 200.4, 136.9, 132.9, 128.5 (2C), 128.0 (2C), 17.6, 38.4, 37.2, 37.1, 27.8, 25.3, 24.1, 22.7, 14.1. HRMS (ESI) *m/z* Calcd for $C_{16}H_{24}O_2Na$ $[M+Na]^+$ 271.1669; Found: 271.1663.



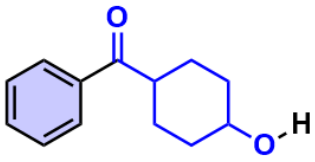
**5-hydroxy-1-phenylpentan-1-one (3ca):** Obtained from tetrahydro-2H-pyran-2-one as the substrate in 75% yield (NMR yield). Yields were determined by $^{1}$H NMR analysis using an internal standard (1,1,2,2-tetrachloroethane). The reaction mixture was purified by Column Chromatography (Hex : EtOAc = 1 : 1, $R_f$ = 0.21) to give the product in 70% isolated yield. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, *J* = 7.2 Hz, 2H), 7.57 (t, *J* = 7.2 Hz, 1H), 7.47 (t, *J* = 7.6 Hz, 2H), 3.68 (t, *J* = 6.4 Hz, 2H), 3.04 (t, *J* = 7.2 Hz, 2H), 1.86 (quin, *J* = 8.0 Hz, 2H), 1.70-1.63 (m, 3H). $^{13}$C NMR (100MHz, $CDCl_3$) δ 200.4, 136.8, 133.0, 128.6 (2C), 128.0 (2C), 62.4, 38.1, 32.2, 20.1. HRMS (ESI) *m/z* Calcd for $C_{11}H_{14}O_2Na$ $[M+Na]^+$ 201.0886; Found: 201.0884.



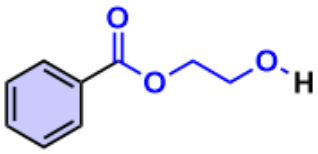
***rac*-2-hydroxy-1-phenylpropan-1-one (3da):** Obtained from DL-lactide as the substrate in 50% yield (NMR yield). Yields were determined by NMR analysis using an internal standard (1,1,2,2-tetrachloroethane). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 42% isolated yield. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.94-7.91 (m, 2H), 7.62 (t, *J* = 7.6 Hz, 1H), 7.50 (t, *J* = 7.6 Hz, 2H), 5.16 (quin, *J* = 6.8, 1H), 3.79 (d, *J* = 6.4 Hz, 1H), 1.44 (d, *J* = 6.8 Hz, 3H). HRMS (ESI) *m/z* Calcd for $C_9H_{10}O_2Na$ $[M+Na]^+$ 173.0573; Found: 173.0574.[a]



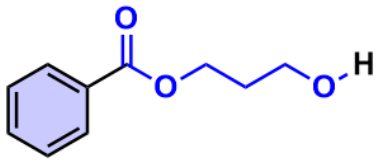
**(*S*)-2-hydroxy-1-phenylpropan-1-one (3da):** Obtained from L-lactide as the substrate in 49% yield (NMR yield). Yields were determined by NMR analysis using an internal standard (1,1,2,2-tetrachloroethane). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 40% isolated yield. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.95-7.90 (m, 2H), 7.61 (t, *J* = 7.6 Hz, 1H), 7.49 (t, *J* = 7.6 Hz, 2H), 5.15 (quin, *J* = 6.8, 1H), 3.80 (d, *J* = 6.4 Hz, 1H), 1.44 (d, *J* = 6.8 Hz, 3H). HRMS (ESI) *m/z* Calcd for $C_9H_{10}O_2Na$ $[M+Na]^+$ 173.0573; Found: 173.0575.[a)]



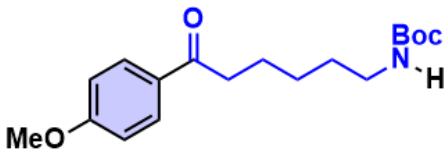
**(4-hydroxycyclohexyl)(phenyl)methanone (3ea):** Obtained from 2-oxabicyclo[2.2.2]octan-3-one as the substrate in 93% yield (NMR yield). Yields were determined by $^{1}$H NMR analysis using an internal standard (1,1,2,2-tetrachloroethane). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 81% isolated yield. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 7.98-7.88 (m, 2H), 7.59-7.42 (m, 3H), 4.05-4.04 (m, 1H), 3.35-3.28 (m, 1H), 2.05-1.64 (m, 9H). $^{13}$C NMR (100MHz, $CDCl_3$) δ 203.4, 136.0, 132.7, 128.5 (2C), 128.1 (2C), 66.0, 44.0, 31.9 (2C), 23.4 (2C). HRMS (ESI) *m/z* Calcd for $C_{13}H_{16}O_2Na$ $[M+Na]^+$ 227.1043; Found: 227.1039.



**2-hydroxyethyl benzoate (3fa):** Obtained from 1,3-dioxolan-2-one as the substrate in 83% yield (GC yield). Yields were determined by GC analysis using an internal standard ($C_{14}H_{30}$). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 69% isolated yield. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, $J$ = 6.8 Hz, 2H), 7.57 (t, $J$ = 7.6 Hz, 1H), 7.44 (t, $J$ = 7.6 Hz, 2H), 4.46 (t, $J$ = 4.8 Hz, 2H), 3.96 (t, $J$ = 4.4 Hz, 2H), 2.40 (broad, 1H). $^{13}$C NMR (100MHz, $CDCl_3$) δ 166.9, 133.1, 129.7, 129.6 (2C), 128.4 (2C), 66.6, 61.3. HRMS (ESI) *m/z* Calcd for $C_9H_{10}O_3Na$ $[M+Na]^+$ 189.0522; Found: 189.0520.



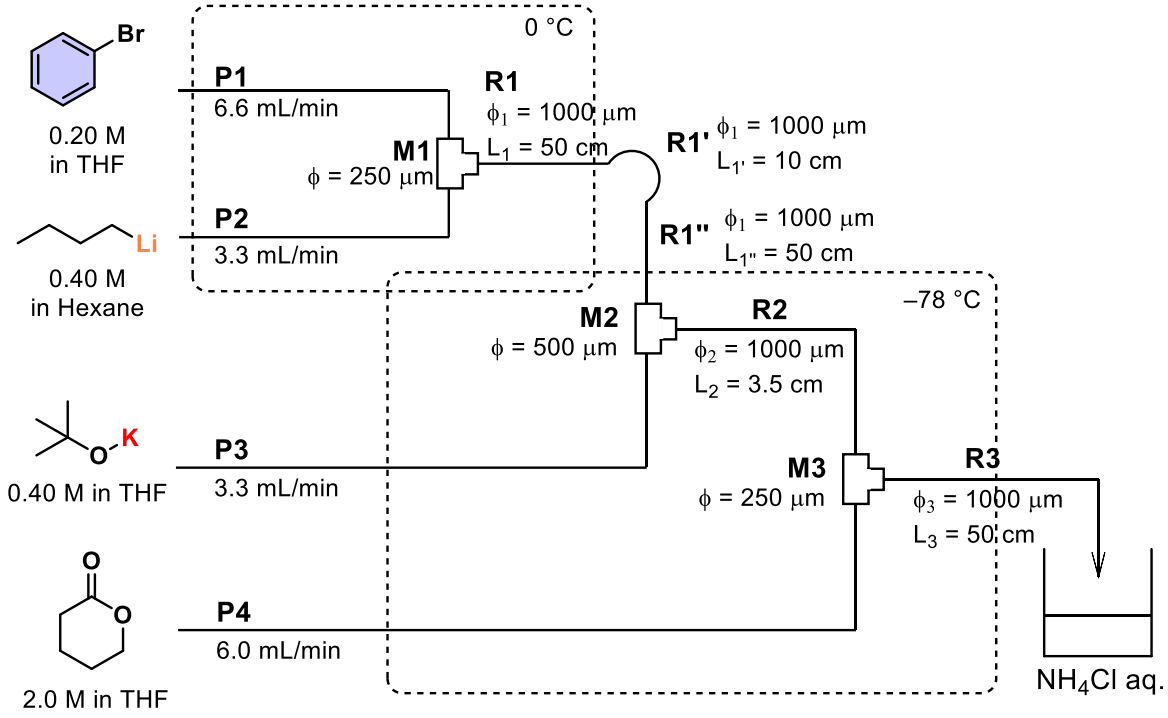
**3-hydroxypropyl benzoate (3ga):** Obtained from 1,3-dioxan-2-one as the substrate in 79% yield (NMR yield). Yields were determined by $^{1}$H NMR analysis using an internal standard (1,1,2,2-tetrachloroethane). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 46% isolated yield. $^{1}$H NMR (400 MHz, $CDCl_3$) δ 8.04 (d, $J$ = 8.4 Hz, 2H), 7.56 (t, $J$ = 7.2 Hz, 1H), 7.44 (t, $J$ = 8.0 Hz, 2H), 4.49 (t, $J$ = 6.0 Hz, 2H), 3.78 (t, $J$ = 6.4 Hz, 2H), 2.40 (broad, 1H), 2.01 (quin, $J$ = 6.0 Hz, 3H). $^{13}$C NMR (100MHz, $CDCl_3$) δ 167.0, 133.0, 130.0, 129.5 (2C), 128.3 (2C), 61.7, 59.0, 31.8. HRMS (ESI) *m/z* Calcd for $C_{10}H_{12}O_3Na$ $[M+Na]^+$ 203.0679; Found: 203.0675.



**tert-butyl (6-(4-methoxyphenyl)-6-oxohexyl)carbamate (3ha):** Obtained from 1-bromo-4-methoxybenzene and tert-butyl 2-oxoazepane-1-carboxylate as the aryl bromide and substrate in 99% yield (NMR yield). Yields were determined by $^{1}$H NMR analysis using an internal standard (1,1,2,2-tetrachloroethane). The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$) to give the product in 80% isolated yield. $^{1}$H NMR (400 MHz,

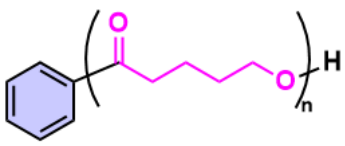
$CDCl_3$) δ 7.95-7.91 (m, 2H), 6.95-6.90 (m, 2H), 3.86 (s, 3H), 3.12-3.09 (m, 2H), 2.91 (t, $J$ = 7.2 Hz, 2H), 1.73 (quin, $J$ = 7.6 Hz, 2H), 1.58-1.35 (m, 14H). $^{13}$C NMR (100MHz, $CDCl_3$) δ 198.7, 163.2, 155.9, 130.1 (2C), 129.8, 113.5 (2C), 78.7, 55.3, 40.2, 37.9, 29.8, 28.2 (3C), 26.4, 24.0. HRMS (ESI) *m/z* Calcd for $C_{18}H_{27}O_4NNa$ $[M+Na]^+$ 344.1832; Found: 344.1824.

### 4-5-9. Synthesis of poly(δ-valerolactone) via Ph[K] in a flow microreactor.



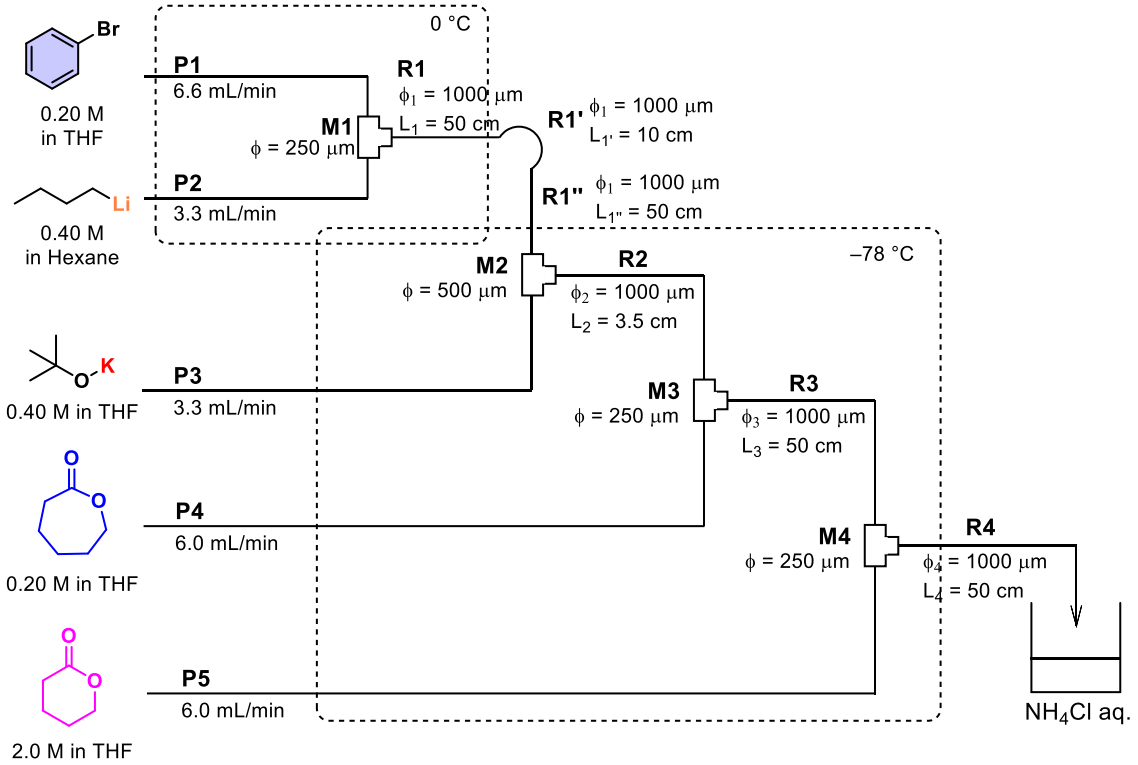

A flow microreactor system consisting of three T-shaped micromixers (**M1**, **M2** and **M3**), five microtube reactors (**R1**, **R1'**, **R1"**, **R2** and **R3**), and four pre-cooling units was used in a cooling bath at 0 °C (**P1** (L = 100 cm) and **P2** (50 cm)) and –78 °C (**P3** (50 cm) and **P4** (100 cm)). A solution of phenyl bromide (0.20 M in THF, flow rate: 6.6 mL/min) and a solution of *n*-BuLi (0.40 M in hexane, flow rate: 3.3 mL/min) were introduced to **M1** ($\phi$ = 250 μm) using syringe pumps, and the mixture was passed through **R1** ($\phi$ = 1000 μm, 50 cm, residence time $t^{R1}$ = 2.4 s), **R1'** ($\phi$ = 1000 μm, 10 cm, residence time $t^{R1'}$ = 0.5 s) and **R1"** ($\phi$ = 1000 μm, 50 cm, residence time $t^{R1"}$ = 2.4 s). The resulting solution was introduced to **M2** ($\phi$ = 500 μm), where a solution of *t*-BuOK (0.40 M in THF) was also introduced (flow rate: 3.3 mL/min). The resulting solution was passed through **R2** ($\phi$ = 1000 μm, L = 3.5 cm, residence time = 0.1 s). The resulting solution was introduced to **M3** ($\phi$ = 250 μm), where a solution of δ-valerolactone (2.0 M in THF) was also introduced (flow rate: 6.0 mL/min). The resulting solution was passed through **R3** ($\phi$ = 1000 μm, L = 50 cm, residence time = 1.2 s). After a steady state was reached, the product solution was collected for 30 seconds. To the aliquot, sat. $NH_4Cl$ aq. was added, and then the organic phase

was analyzed by GPC and NMR.



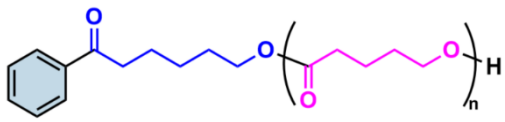
**oligomer 5ca:** The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.90-7.88 (m, 2H), 7.52-7.50 (m, 1H), 7.43-7.40 (m, 2H), 4.08-4.02 (m, 51H), 3.62-3.55 (m, 2H), 2.98-2.94 (m, 2H), 2.44-2.13 (m, 51H), 1.77- 1.37 (m, 107 H). GPC $M_n$: 4879, PDI:1.36.

### 4-5-10. Synthesis of a sequence oligomer in a flow microreactor.



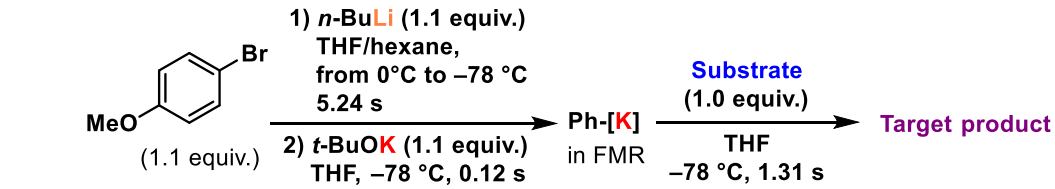

A flow microreactor system consisting of four T-shaped micromixers (**M1**, **M2, M3** and **M4**), six microtube reactors (**R1**, **R1'**, **R1"**, **R2**, **R3** and **R4**), and four pre-cooling units was used in a cooling bath at 0 °C (**P1** (L = 100 cm) and **P2** (50 cm)) and –78 °C (**P3** (50 cm), **P4** (100 cm) and **P5** (100 cm)). A solution of phenyl bromide (0.20 M in THF, flow rate: 6.6 mL/min) and a solution of *n*-BuLi (0.40 M in hexane, flow rate: 3.3 mL/min) were introduced to **M1** ($\phi$ = 250 μm) using syringe pumps, and the mixture was passed through **R1** ($\phi$ = 1000 μm, 50 cm, residence time $t^{R1}$ = 2.4 s), **R1'** ($\phi$ = 1000 μm, 10 cm, residence time $t^{R1'}$ = 0.5 s) and **R1"** ($\phi$ = 1000 μm, 50 cm, residence time $t^{R1"}$ = 2.4 s). The resulting solution was introduced to **M2** ($\phi$ = 500 μm), where a solution of *t*-BuOK (0.40 M in THF) was also introduced (flow rate: 3.3 mL/min). The resulting solution was passed through **R2** ($\phi$ = 1000 μm, L = 3.5 cm, residence time = 0.1 s). The resulting solution was introduced to **M3** ($\phi$ = 250 μm), where a solution of ε-caprolactone (0.20 M in THF) was also introduced (flow rate: 6.0 mL/min). The resulting solution was passed through **R3** ($\phi$ =

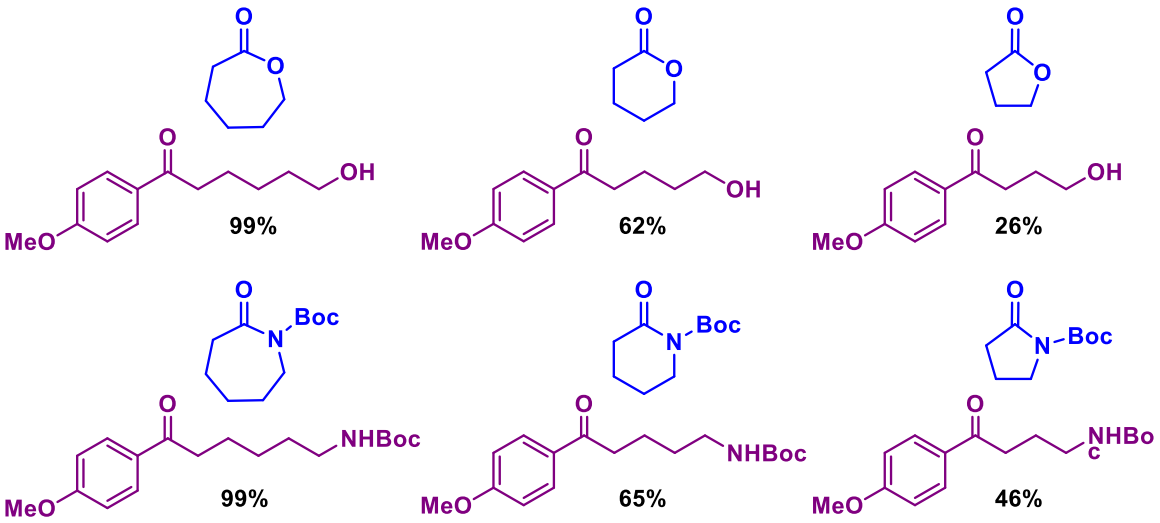
1000 μm, L = 50 cm, residence time = 1.2 s). The resulting solution was introduced to **M4** ($\phi$ = 250 μm), where a solution of δ-valerolactone (2.0 M in THF) was also introduced (flow rate: 6.0 mL/min). The resulting solution was passed through **R4** ($\phi$ = 1000 μm, L = 50 cm, residence time = 0.9 s). After a steady state was reached, the product solution was collected for 30 seconds. To the aliquot, sat. $NH_4Cl$ aq. was added, and then the organic phase was analyzed by GPC and NMR.



**oligomer 6:** The reaction mixture was purified by Gel Permeation Chromatography (GPC, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$) δ 7.97-7.96 (m, 2H), 7.59-7.55 (m, 1H), 7.49-7.45 (m, 2H), 4.10-4.07 (m, 35H), 3.67-3.64 (m, 2H), 3.02-2.98 (m, 2H), 2.44-2.33 (m, 35H), 1.82-1.41 (m, 85H). GPC $M_n$: 3669, PDI:1.31.

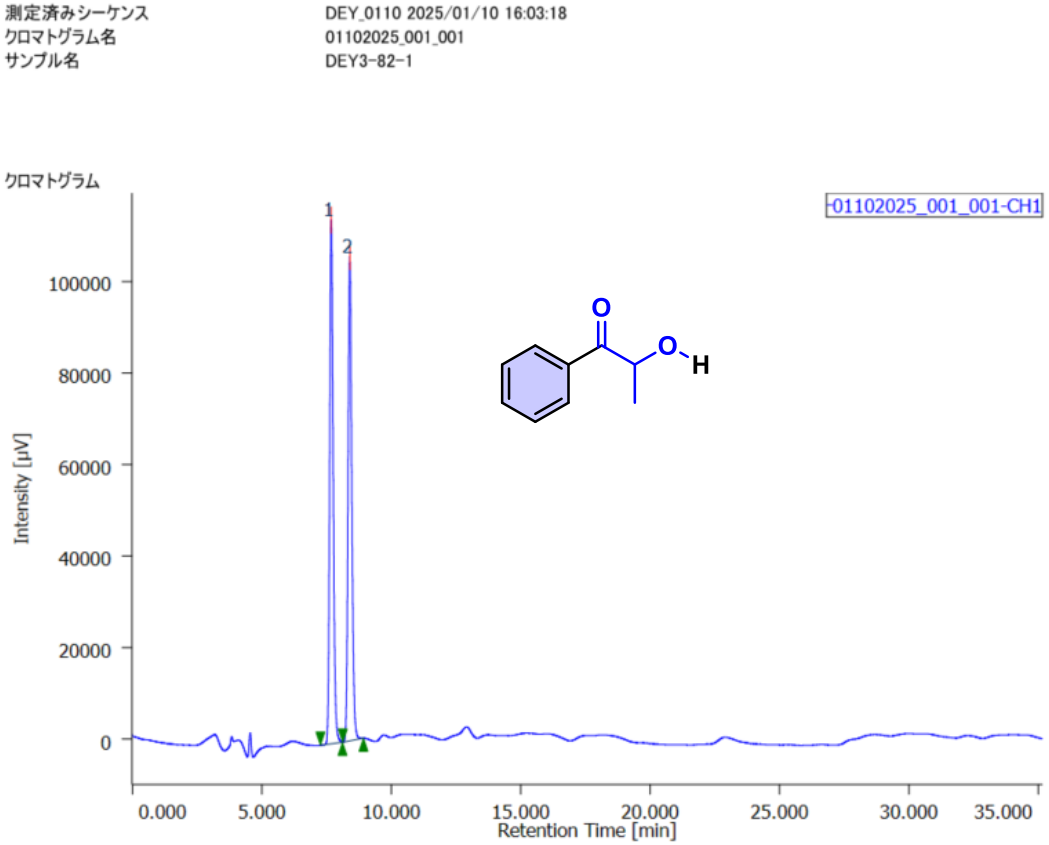
### 4-5-11. Scope of various lactones, cyclic carbonates, and lactams on ring-opening monoaddition in a flow microreactor.



### 4-5-12. Chiral HPLC analyses.

The ee was determined on a CHIRALPAK® IA column with hexane/*iso*-propyl alcohol = 95/5, flow =1.0 mL/min, wavelength = 254 nm. Retention times: 7.7 min (50.3%), 8.4 min (49.7%).




クロマトグラム情報

| | |
|---|---|
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| システム名 | HPLC – JASCO |
| 測定日 | 2025/01/10 16:04:20 |
| 注入量 | 1.00 [μL] |
| サンプル# | 1 |
| プロジェクト名 | okamoto |
| 取込時間 | 60.0 [min] |
| 測定シーケンス | |
| コントロールメソッド | okamoto |

チャンネル情報

| | |
|---|---|
| クロマトグラム名 | 01102025_001_001-CH1 |
| サンプル名 | DEY3-82-1 |
| 波形処理メソッド | (マニュアル) |

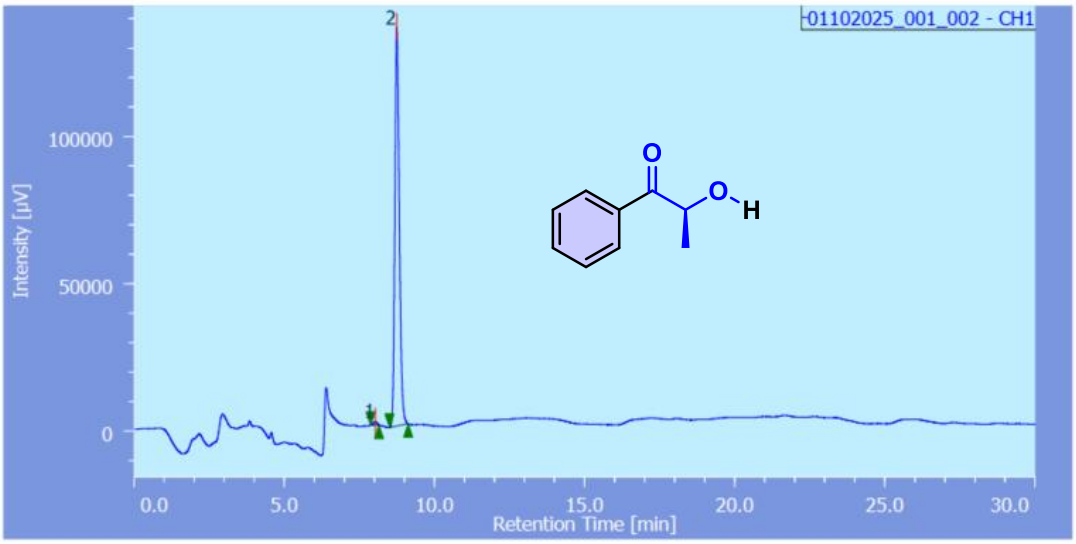
ピーク情報

| # | ピーク名 | CH | tR [min] | 面積 [μV·sec] | 面積% |
|---|---|---|---|---|---|
| 1 | Unknown | 1 | 7.683 | 1087379 | 50.254 |
| 2 | Unknown | 1 | 8.398 | 1076374 | 49.746 |

**Figure 5.** Chiral HPLC analysis of *rac*-2-hydroxy-1-phenylpropan-1-one.

The ee was determined on a CHIRALPAK® IA column with hexane/*iso*-propyl alcohol = 95/5, flow =1.0 mL/min, wavelength = 254 nm. Retention times: 8.0 min (0.7%), 8.7 min (99.3%).

クロマトグラム




| | |
|---|---|
| クロマトグラム情報 | |
| ユーザー名 | JASCO |
| 更新日時 | 2025/01/10 17:11:36 |
| コメント | IB hex/IPA = 95:5 1.0mL/min 254 nm |
| HPLC システム名 | HPLC - JASCO |
| 測定日 | 2025/01/10 16:41:34 |
| 注入量 | 1.00 [μL] |
| サンプル# | 1 |
| プロジェクト名 | okamoto |
| 取込時間 | 30.0 [min] |
| 測定シーケンス | |
| コントロールメソッド | okamoto |
| ピーク ID テーブル | |
| 検量線テーブル | |
| 追加情報 | |

| | |
|---|---|
| チャンネル情報＋ピーク情報 | |
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| サンプル名 | DEY3-82-1 |
| チャンネル名 | UV-2075 |
| データ取り込み間隔 | 100 [msec] |
| 波形処理メソッド | (マニュアル) |
| 数値計算式 | |
| 判定式 | |

| # | ピーク名 | CH | tR [min] | 面積 [μV·sec] | 高さ [μV] | NTP | 分離度 | シンメトリー係数 | 面積% | 高さ% |
|---|---|---|---|---|---|---|---|---|---|---|
| 1 | Unknown | 1 | 8.023 | 10073 | 1196 | 18915 | 2.885 | 0.937 | 0.709 | 0.875 |
| 2 | Unknown | 1 | 8.747 | 1409855 | 135495 | 16855 | N/A | 1.214 | 99.291 | 99.125 |

**Figure 6.** Chiral HPLC analysis of (*S*)-2-hydroxy-1-phenylpropan-1-one.

# Conclusion

In this thesis, a flash-flow synthetic system was developed to achieve selective living anionic monoaddition under 1:1 stoichiometric control of highly reactive organometallic species and polymerizable monomers, taking advantage of rapid mixing, precise residence-time control, and efficient heat transfer. This strategy was further extended to an integrated one-flow system, in which multiple monomers were introduced sequentially, enabling the synthesis of sequence-defined oligomers with carbon–carbon bond backbones.

In Chapter 2, a flash-flow monoaddition of vinyl monomers such as styrenes and methacrylates, initiated by sec-butyllithium, was achieved in a flow microreactor. Rapid mixing effectively suppressed undesired oligomerization, enabling selective 1:1 addition between the initiator and the monomer. Furthermore, by sequentially introducing the initiator, multiple vinyl monomers, and electrophiles for terminal functionalization, sequence-defined oligomers consisting of up to six components were synthesized within seconds and in high yields. In addition, incorporation of selected vinyl monomers as oligomeric blocks did not disrupt the sequence, enabling the synthesis of structurally diverse oligomers with a defined molecular sequence.

In Chapter 3, the rapid and quantitative generation of benzophenone dianion (BPD) was generated under flow conditions, and its application as a novel initiator for living anionic monoaddition was established. Using alkali-metal naphthalenides as reducing agents, BPD was selectively generated and subsequently reacted with methacrylates to afford monoadducts with high selectivity. Millisecond-scale rapid mixing effectively suppressed side reactions, and introduction of electrophiles at the reaction terminus enabled the selective formation of structurally diverse monoadducts. Furthermore, broad substrate scope was demonstrated across various benzophenone derivatives and methacrylates, and the strategy was shown to be extendable to the synthesis of sequence-defined oligomers. This study expands the scope of molecular sequence construction strategies utilizing benzophenone dianion as an initiator.

In Chapter 4, the flash generation of organopotassium species and their selective anionic ring-opening monoaddition to lactones were demonstrated. Through precise reaction control using a flow microreactor, Schlosser base was employed to selectively generate aryl potassium nucleophiles bearing base-sensitive substituents. This approach effectively suppressed side reactions and enabled highly selective ring-opening monoaddition. The living anionic terminus was maintained throughout the reaction. Using this controlled system, sequence-defined oligomers were synthesized by sequentially introducing different lactones. This study provides a synthetic strategy for the precise control of organopotassium species and advances sustainable polyester synthesis and anionic ring-opening polymerization.

In summary, this thesis presents a synthetic strategy for the construction of sequence-defined synthetic polymers based on flow-controlled living anionic monoaddition. Beyond the development of a sequence control strategy, this work demonstrates the potential of flow technology for the precise control of highly reactive organometallic species. This study contributes to the fields of synthetic organic chemistry, polymer chemistry, and flow chemistry, and is expected to provide an important foundation for future advances in molecular coding, functional material design, and sustainable polymer synthesis.

## References


1) K. Okamoto, **D. Yoo**, R. Yoshioka, R. Nakasato, Y. Ashikari, K. Kitayama, A. Nagaki, *Angew. Chem. Int. Ed.*, **2025**, *64*, e202416875. (*chapter 2*)
2) **D. Yoo**, K. Okamoto, A. Nagaki, *Chem. Eur. J.*, **2025**, in revision. (*chapter 3*)
3) **D. Yoo**, K. Okamoto, M. Takeda, H. Nakayama, R. Ebisawa, A. Nagaki, *ChemSusChem*, **2025**, *19*, e202502201. (*chapter 4*)


## Other publications


1) Y. Ashikari, R. Yoshioka, Y. Yonekura, **D. Yoo**, K. Okamoto, A. Nagaki, *Chem.*, **2024**, *30*, e202303774.
2) H. Soutome, Y. Kimuro, T. Kawaguchi, **D. Yoo**, Y. Yao, S. Oshida, H. Nakayama, M. Iwata, R. Ebisawa, R. Kikuchi, K. Tomite, S. Wada, Y. Ashikari, A. Nagaki, *Synthesis*, **2024**, *56*, 821–827.

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