Rapid Electrochemical Synthesis via Cationic Intermediates in Flow

Masahiro Takumi

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Preface

The studies presented in this doctoral thesis have been carried out under the direction of Professor Aiichiro Nagaki and Professor Jun-ichi Yoshida at the Department of Synthetic Chemistry and Biological Chemistry of Kyoto University during 2012-2015 and 2018-2022. The studies are concerned with rapid organic synthesis based on electrochemically generated cationic intermediates using a flow electrochemical reactor system.

The author would like to express his sincerest gratitude to Professor Aiichiro Nagaki and Professor Jun-ichi Yoshida for their kind guidance and valuable discussions throughout this work. The author appreciates the circumstance to investigate in the field of the chemistry. The author deeply appreciates to Professor Toshiki Nokami, Dr. Akihiro Shimizu, Dr. Keisuke Asano, and Dr. Yosuke Tani for their helpful advice.

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Contents

General Introduction

Organic synthesis has contributed tremendously toward the progress of all fields of science and technology by creating various biologically active compounds and functional materials. Rapid progress in such fields demands production and supply of the desired compounds in a highly time-efficient manner, for which organic synthesis must be accelerated. However, conventional organic synthesis still has been based on slow reactions and lengthy reaction processes because fast reactions are difficult or practically impossible to control. Therefore, the development and implementation of methodologies to control fast reactions in a controlled way has been strongly needed.

Organic cations, such as carbenium ions and onium ions, are important reactive intermediates and play a crucial role in organic chemistry.[1] They are central to the mechanistic and quantitative understanding of organic chemistry and contribute to the progress of organic synthesis by enabling fast and unique reactions. In general, they are highly unstable, generated in the presence of nucleophiles by Brønsted or Lewis acids and immediately consumed. This limitation of organic cations is a major obstacle for their use in organic synthesis, and nucleophiles that do not survive under such acidic conditions cannot be used. By contrast, organic anions, such as organolithiums and organomagnesiums, can usually be generated and accumulated in solution in the absence of electrophiles, and a subsequent reaction with an electrophile can be conducted after the generation process is complete. Thus, the development of new methodologies that enable the generation of organic cations in the absence of nucleophiles has widened the scope of organic cation chemistry and received immense research interest. Considering the need for achieving rapid synthesis and production, it is desirable to complete the cation generation process in the shortest possible time.

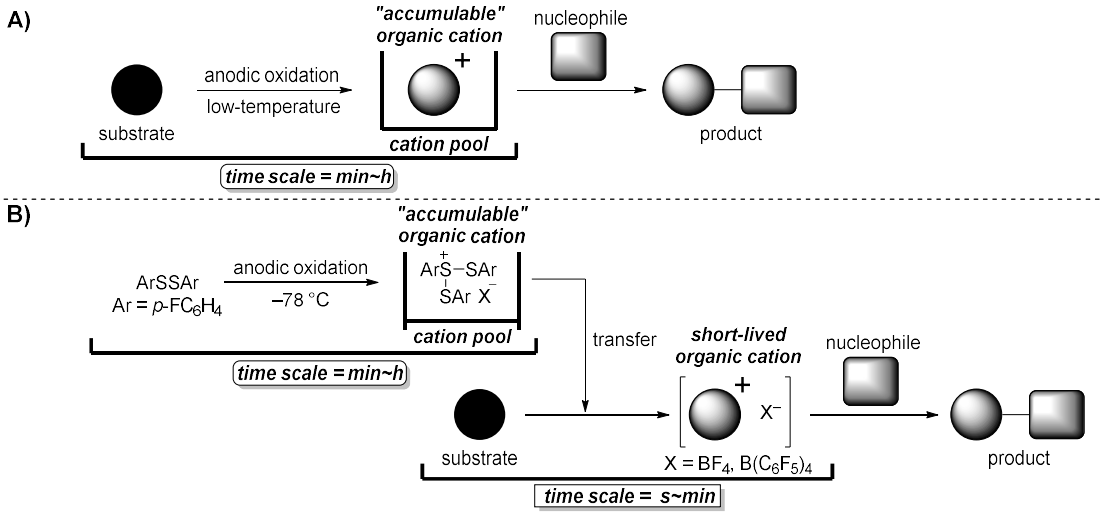
Organic electrochemistry is a long-established methodology and provides numerous opportunities for exploring and developing novel synthetic transformations.[2] Electrolysis can generate highly reactive intermediates such as cations, anions, and radicals via forced single electron transfer between the electrode and substrate. In this process, electrons serve as traceless redox reagents, thereby avoiding the use of hazardous chemical reductants and oxidants and offering green reaction conditions. Considering these advantages, organic electrochemistry has been recognized as essential for the development of organic synthesis in the 21st century.[3]

Electrochemical oxidation offers a powerful method for synthesizing and modifying organic molecules.[4] One of the greatest advantages of this technique lies in generating highly reactive organic cations because the anodic process utilizes neutral reaction

conditions, allows irreversible generation, and employs supporting electrolytes as tunable counteranion donors for changing the reactivity of the generated cations. Therefore, the use of electrochemical oxidation can open up entirely new strategies for the synthesis of complex molecules via organic cations.

In 1999, Yoshida et al. developed an electrochemical oxidation method called the cation pool method, enriching the field of electrochemistry and the chemistry of organic cations.[5] This method involves generation and accumulation of organic cations in the absence of nucleophiles under cryogenic temperature such as –78 °C using electrochemical divided-type batch reactor (Scheme 1A). After electrolysis, the accumulated cations can be used for subsequent reactions with nucleophiles and are directly observed using NMR spectroscopy. Starting with the report on *N*-acyliminium ions,[6] this method has been applied to various organic cations, such as oxocarbenium ions,[7] diarylcarbenium ions[8] and arylbis(arylthiol)sulfonium ions.[9] The applicability of this method is determined by the stability of generated cations, where the lifetime of generated cations is sufficiently longer than the total electrolysis time. This is because electrolysis takes several hours to achieve completion; it is a heterogeneous process that occurs only on the surface of an electrode. The "indirect cation pool"[10] and "indirect cation flow"[11] method rapidly generate organic cations within a few minutes mediated by anodically generated arylbis(arylthiol)sulfonium ions; however, this strategy still relies on the accumulable cations (Scheme 1B). Therefore, shortening the electrolysis time would be a key to the progress of the organic electrochemistry.

Scheme 1. (A) Cation Pool Method, (B) Indirect Cation Pool Method and Indirect Cation Flow Method.



Recently, flow electrochemical reactors, a combined technology of flow chemistry and electrochemistry, have received significant research interest in both academia and industry.[12] Due to their high mass and heat transfer ability, electrolysis can be caried out with great precision and reproducibility. Possible downsizing of the reactor offers high surface-to-volume ratio of the electrodes and narrow interelectrode gaps, both contributing to electrolysis efficiency. These features are advantageous for acceleration of electrochemical reactions involving unstable reactive intermediates.

On application involving a flow electrochemical reactor, Yoshida et al. developed a divided-type flow electrochemical reactor that can electrochemically generate *N*-acyliminium ions at low-temperature (Scheme 2A).[13] The generated organic cations are immediately transferred to another location where a reaction with nucleophile gives the desired coupling product. Later, this approach was extended to paired electrolysis involving anodic generation of organic cations and cathodic generation of carbanion equivalents.[14] In this work, anodically generated *N*-acyliminium ions were reacted with cathodically generated cinnamyltrimethylsilanes downstream to afford the coupling product. In these studies, although a slow flow rate led a prolonged reaction time for product formation, the system allowed continuous sequential combinatorial synthesis by simple flow switching.

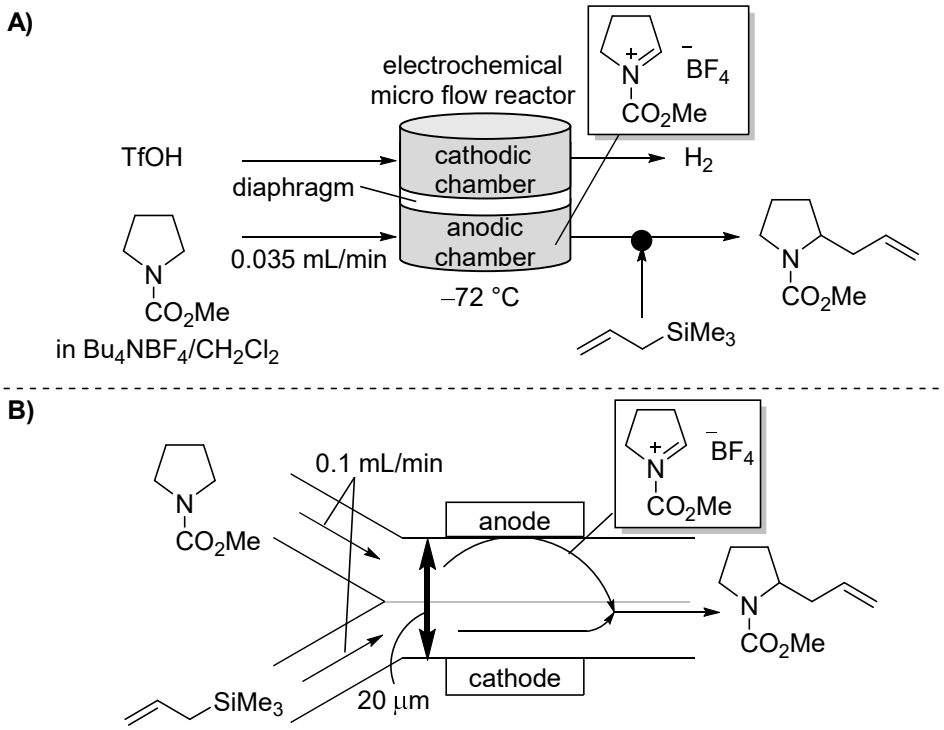
In another important example, Atobe et al. developed a two-inlet microflow electrochemical reactor with an interelectrode gap of 20 μm, which renders a parallel laminar flow in the reactor, and demonstrated the selective anodic generation of *N*-acyliminium ions and subsequent trapping reaction with an easily oxidizable carbon nucleophile (Scheme 2B).[15] By using two inlets, the stream containing the *N*-(methoxycarbonyl)pyrrolidine can be selectively directed over the anode while the allyltrimethylsilane is passed over the cathode. This allows for selective formation of the carbocation which can subsequently diffuse to cathodic side and react with the nucleophile to give the desired product in excellent yield. This elegant approach has allowed a variety of electrochemical transformations, including aromatic C−C cross-coupling reaction[16] and generation of electrogenerated base such as 2-pyrrolidone anions.[17]

Since the 2010s, there has been a remarkable progress in this field supported by the development of equipment and methodologies (Scheme 3). Especially in Europe, numerous chemists have been conducting research focused on implementing this environmentally friendly methodology into the industrial production process.

Wirth et al. developed an undivided flow electrochemical reactor and achieved efficient utilization of unstable hypervalent iodine reagents (Scheme 3A).[18] The hypervalent iodine reagents were electrooxidatively generated from aryl iodides without external chemical oxidants. In their integrated flow system, the generated unstable hypervalent iodine reagents could be immediately used as mediators for valuable chemical transformations

such as fluorinations or heterocycle formations.

Scheme 2. (A) Cation Flow Method, (B) Selective Anodic Substitution Reaction Under Parallel Laminar Flow.



Waldvogel et al. developed various highly modular flow electrochemical reactors and demonstrated their diverse application in electroorganic synthesis.[19] The devices facilitate adjustment of the interelectrode gap and exchange of electrode materials. The anodic dehydrogenative cross-couplings of phenols using the boron-doped diamond (BDD) electrode developed in batch reactor was successfully applied to the flow module and scaled-up (Scheme 3B). Notably, not only the reproducibility was improved by the external cooling circuit, but also the supporting electrolyte was significantly or completely reduced by adjusting interelectrode gap.

Noël et al. developed a flow electrochemical microreactor that can modulate the reactor volume and demonstrated the electrooxidative coupling of amines and thiols (Scheme 3C).[20] The reaction time could be dramatically reduced from 24 h in batch to 5 min due to the shorter diffusion distances, large electrode-surface-to-volume ratio, and increased mass transfer. In another application to the sulfonyl fluoride synthesis in biphasic media, the efficient formation of segments and narrow interelectrode gap in the microreactor facilitated the reduction in reaction time.[21] In their reports, the reactor volume and the electrolysis time can be varied by attaching and removing the flow channel loops, revealing

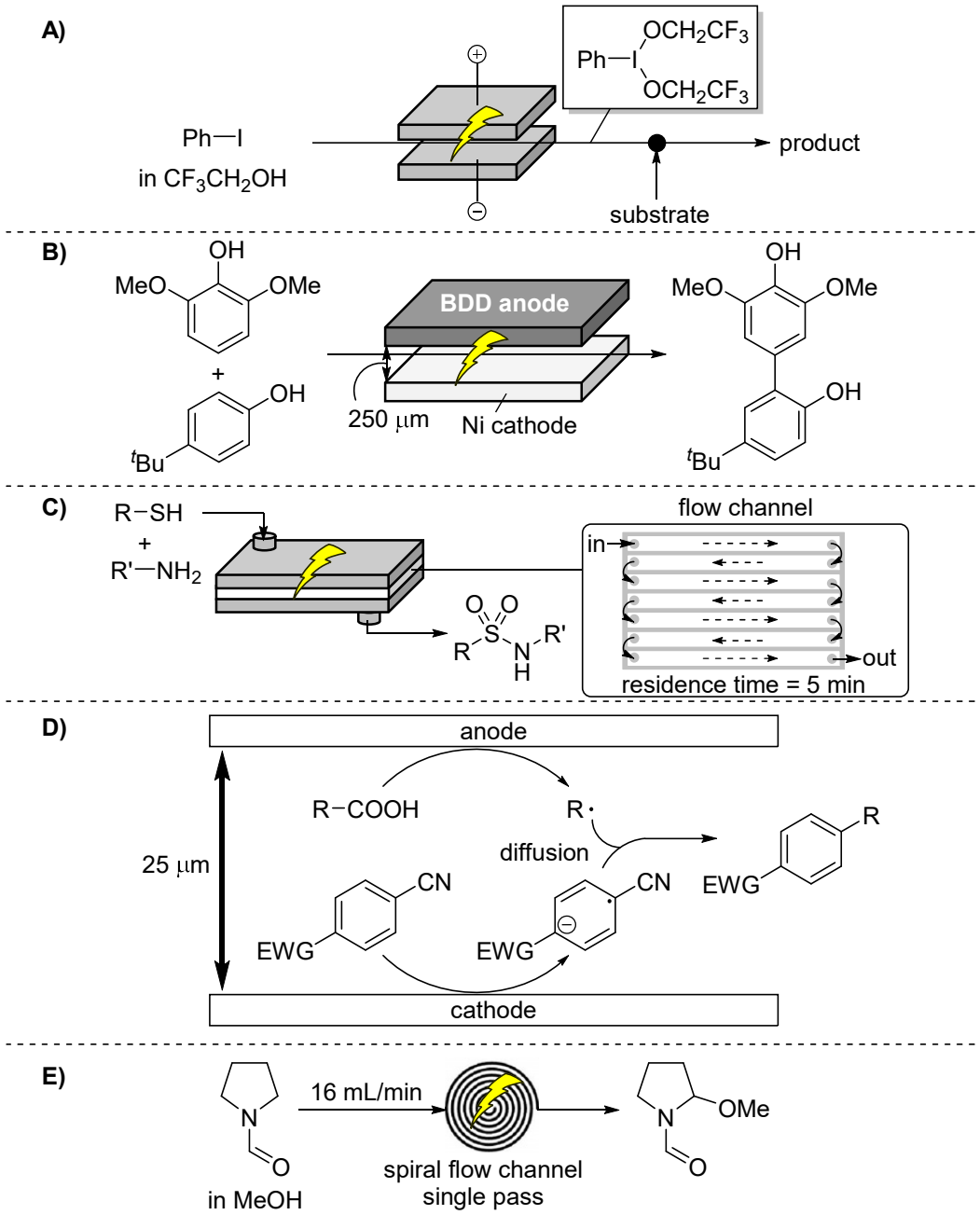
the kinetic information of the electrochemical reaction. Moreover, the operating mode can be changed from serial to parallel. The parallel mode facilitates the scaling up of the reaction via numbering-up strategy or simultaneously scanning different reaction conditions. The latter aspect was used to rapidly find optimal reaction conditions for the electrocatalytic reduction of furfural to furfuryl alcohol.[22]

Jensen et al. achieved elegant radical-radical cross-coupling reaction by performing paired electrolysis in microchannels (Scheme 3D).[23] The oxidation of carboxylic acids to primary alkyl radicals was coupled with the reductive formation of radical anions, providing corresponding cross-coupling products. Selective cross-coupling was facilitated by the rapid molecular diffusion across a flow channel with interelectrode gap of 25 μm that suppresses the decomposition of the radicals. In addition, the developed platform was shown to enable a gram-scale electrosynthesis of a liquid crystal compound, demonstrating its high practicality.

Achieving high conversion in a single pass under high flow rate conditions is a key development goal for rapid synthesis and production. Pletcher and Brown developed undivided flow electrochemical reactors having snake-[24] or spiral-shaped[25] channels with extended channel length. They demonstrated the anodic methoxylation of *N*-formylpyrrolidine with the almost quantitative conversion through the spiral reactor using a flow rate of 16 mL/min and productivity reached >20 g/h (Scheme 3E). Recently, the protocol was extended to the electrochemical functionalization of cubane by oxidative decarboxylative ether formation (Hofer–Moest reaction) providing precursor of cubanisidine biosiostere building blocks, thereby promising analogues in the field of medicine and material chemistry.[26]

While significant progress has been made during the past decade, the low efficiency of flow electrolysis and slow flow rate that prolong the electrolysis process remains challenging. It is envisioned that the development of an electrolysis-compatible flow electrochemical reactor with high electrolysis efficiency under high flow rate conditions would potentially enable extremely fast generation of short-lived reactive intermediates. These intermediates could be directly used for subsequent reactions without their decomposition and would contribute immensely to the progress of organic electrosynthesis and production using reactive intermediates.

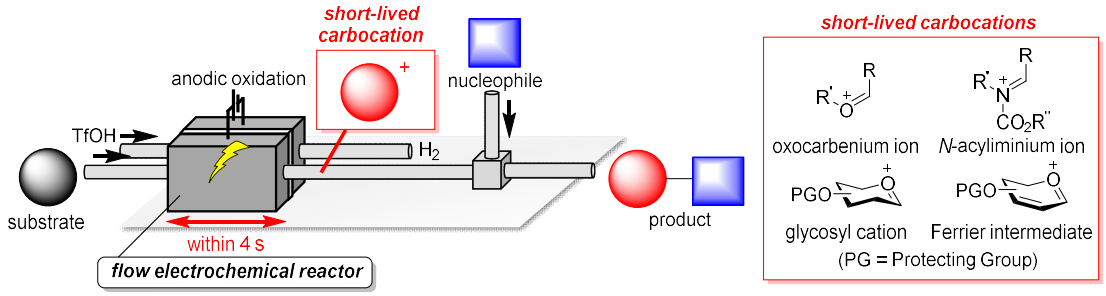
Scheme 3. (A) Electrochemical Generation and Utilization of Hypervalent Iodine Reagents Under Flow Conditions. (B) Anodic Cross-Coupling Reaction of Phenols in Highly Modular Flow Reactor. (C) Electrooxidative Coupling of Thiols and Amines in Flow. (D) Redox-Neutral Cross-Coupling Reaction of Unstable Radicals in Flow. (E) Electrochemical Methoxylation of *N*-Formylpyrrolidine in a Spiral Flow Channel.



This doctoral thesis focuses on the combined technology of electrochemistry and flow chemistry to rapidly synthesize complex organic molecules and macromolecules using highly reactive organic cations.

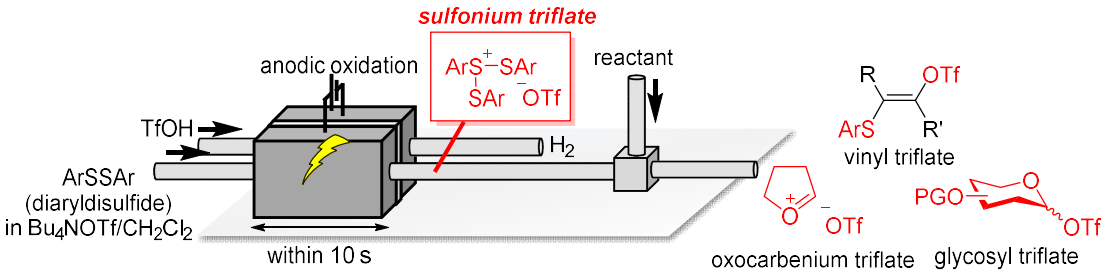
In chapter 1, the development and utilization of a novel flow electrochemical reactor that can accomplish electrolysis within a few seconds is described (Scheme 4). Flash (extremely fast) generation of short-lived carbocations is successfully achieved with an electrochemical oxidation in a single passage of reactants through the reactor, enabling the subsequent reaction with nucleophiles before the decomposition of the carbocations. The methodology is applied to a variety of highly reactive carbocations such as oxocarbenium ions, *N*-acyliminium ions, glycosyl cations, and Ferrier intermediates. Moreover, continuous and rapid production of a pharmaceutical precursor using the flow reactor system was successfully demonstrated.

Scheme 4. Flash Electrochemical Approach to Short-Lived Carbocations Using a Flow Electrochemical Reactor System.



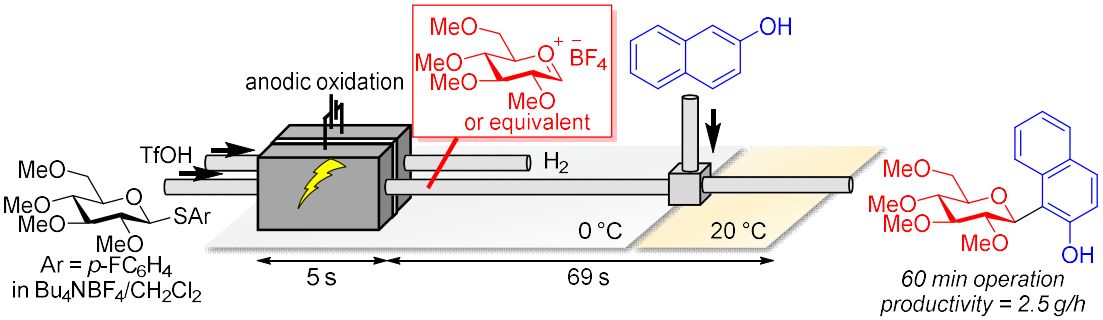
In chapter 2, a rapid approach to reactive organic triflates based on the flash electrochemical generation of arylbis(arylthio)sulfonium triflates is described (Scheme 5). Flash generation of highly unstable sulfonium triflates within 10 seconds using a flow electrochemical reactor was achieved, enabling one-flow access to vinyl triflates, short-lived oxocarbenium triflates, and glycosyl triflates.

Scheme 5. Flash Electrochemical Generation of Arylbis(arylthio)sulfonium Triflates and Their Direct Utilization for Organic Triflates Synthesis.



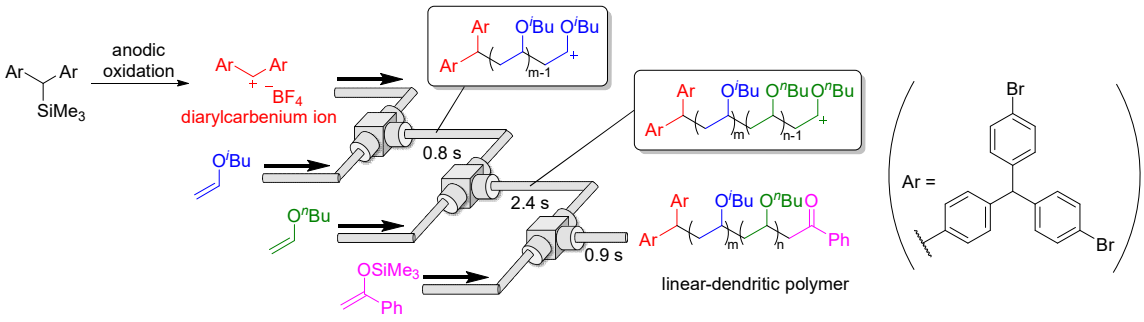
In chapter 3, continuous and rapid production of *C*-arylglycosides using a flow electrochemical reactor system is described (Scheme 6). Anodic oxidation of thioglycosides in the Bu_4NBF_4/CH_2Cl_2 system followed by the reaction with phenols gives corresponding *C*-arylglycoside in good yield. The features of the flow electrochemical reactor, such as rapid electrolysis performance, narrow interelectrode gap, and precise temperature controllability allow faster and greener approach to obtain desired products compared to the conventional batch reactor.

Scheme 6. Continuous and Rapid Production of *C*-Arylglycosides Based on Flash Electrolysis Using a Flow Electrochemical Reactor System.



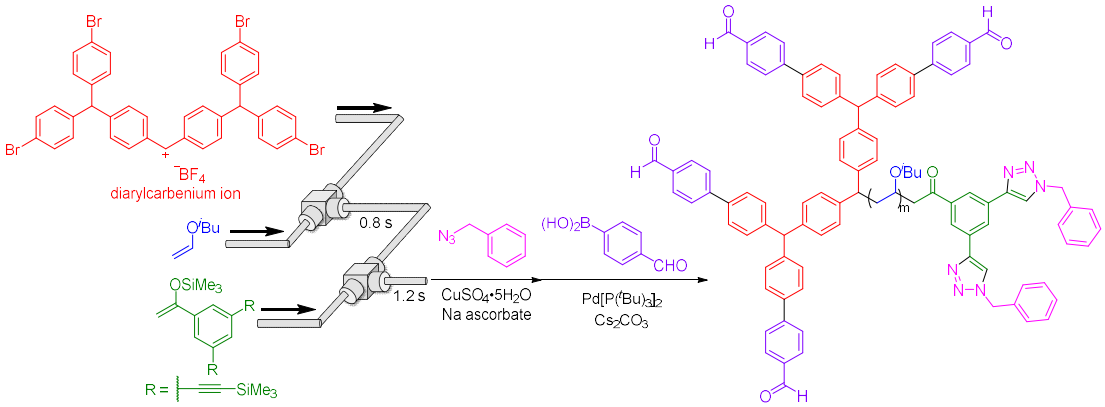
In chapter 4, flash cationic polymerization of vinyl ethers initiated by a reactive dendritic diarylcarbenium ion using a flow microreactor system is described (Scheme 7). Fast mixing in a micromixer is effective in controlling the initiation of cationic polymerization, providing linear-dendritic polymers with controlled molecular weights and narrow molecular weight distributions. The cationic living end is efficiently used for trapping reaction with various carbon nucleophiles and for block copolymerization by residence time control to give structurally well-defined linear-dendritic polymers.

Scheme 7. Flash Cationic Polymerization of Vinyl Ethers Initiated by a Dendritic Diarylcarbenium Ion.



Chapter 5 describes the cationic polymerization of vinyl ethers using multifunctional initiator and terminator in a flow microreactor system, giving polymers with multiple functionalities on both ends (Scheme 8). Subsequent transformation of the resulting polymers through Suzuki-Miyaura coupling and/or copper-mediated azide-alkyne cycloaddition is also accomplished to give linear-dendritic hybrid polymers.

Scheme 8. Linear-Dendritic Hybrid Polymer Synthesis Based on Flash Cationic Polymerization of Vinyl Ethers Using a Multifunctional Dendritic Initiator and Multifunctional Terminators.



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Chapter 1

Flash Electrochemical Approach to Carbocations Using a Flow Electrochemical Reactor System

Abstract

A novel divided-type flow electrochemical reactor that accomplishes electrolysis within a few seconds was developed. The flash (extremely fast) electrolysis in the flow reactor system enabled flash generation of various short-lived carbocations such as oxocarbenium ions, *N*-acyliminium ions, glycosyl cations and Ferrier intermediates, and the subsequent reaction with nucleophiles before their decomposition. Moreover, multi gram-scale production of a pharmaceutical precursor was successfully achieved by continuous operation based on the present flow system.

Introduction

Unstable reactive intermediates such as cations, anions and radicals are recognized as extremely powerful and versatile tools in synthetic chemistry.[1] To maximize their high reactivity in molecular transformations, careful and precise reaction strategies are required. In fact, a number of synthetic methods have been developed and extensively studied even today. Among them, one novel synthetic approach based on the concept of flash chemistry[2] has attracted significant attention in recent years. Flash chemistry is an innovative methodology by which, using a flow microreactor,[3] extremely unstable reactive intermediates were generated and used for subsequent reactions within a few milliseconds time scale, "in a flash of time" (Figure 1A).[4] By implementing this methodology, molecular transformations, which would have previously been impossible in conventional batch reactors, have been successfully achieved using short-lived carbanions chemically derived from highly reactive organometallic reagents such as organolithiums.[5]

Electrochemical approaches to the generation and utilization of reactive intermediates have also been studied as extensively as chemical methods.[6] Compared with chemical methods, electrochemical methods have two advantageous features. One is that the method is quite straightforward because electrons serve as traceless redox reagents instead of harmful chemical reagents. The other is that forced electron transfer between electrodes and substrates allows irreversible generation of reactive intermediates. For these features, electrochemical methods are recognized as highly attractive to utilize reactive intermediates. However, conventional batch electrochemical reactors are difficult or impossible, in principle, to approach short-lived intermediates within a short period because the electrolysis is a heterogeneous reaction process and the small surface-to-volume ratio of the electrodes entails a long electrolysis duration (Figure 1B).

In recent years, research into the combination of electrochemistry and flow chemistry has gained a lot of attraction among researchers in both academia and industry. This new technology, flow electrochemical reactors have been recently developed and reported as promising synthetic devices for improving reaction efficiency and productivity.[7] Nevertheless, in many cases, the unsatisfactory electrolysis efficiency in flow often mandates slow flow rate, long channel length and recycling of substrate solutions, requiring long electrolysis times. If an flow-compatible electrochemical reactor having fast and high electrolysis efficiency was newly developed, it would be possible to achieve flash generation and utilization of highly reactive intermediates. This methodology could lead to flash electroorganic chemistry (Figure 1C).

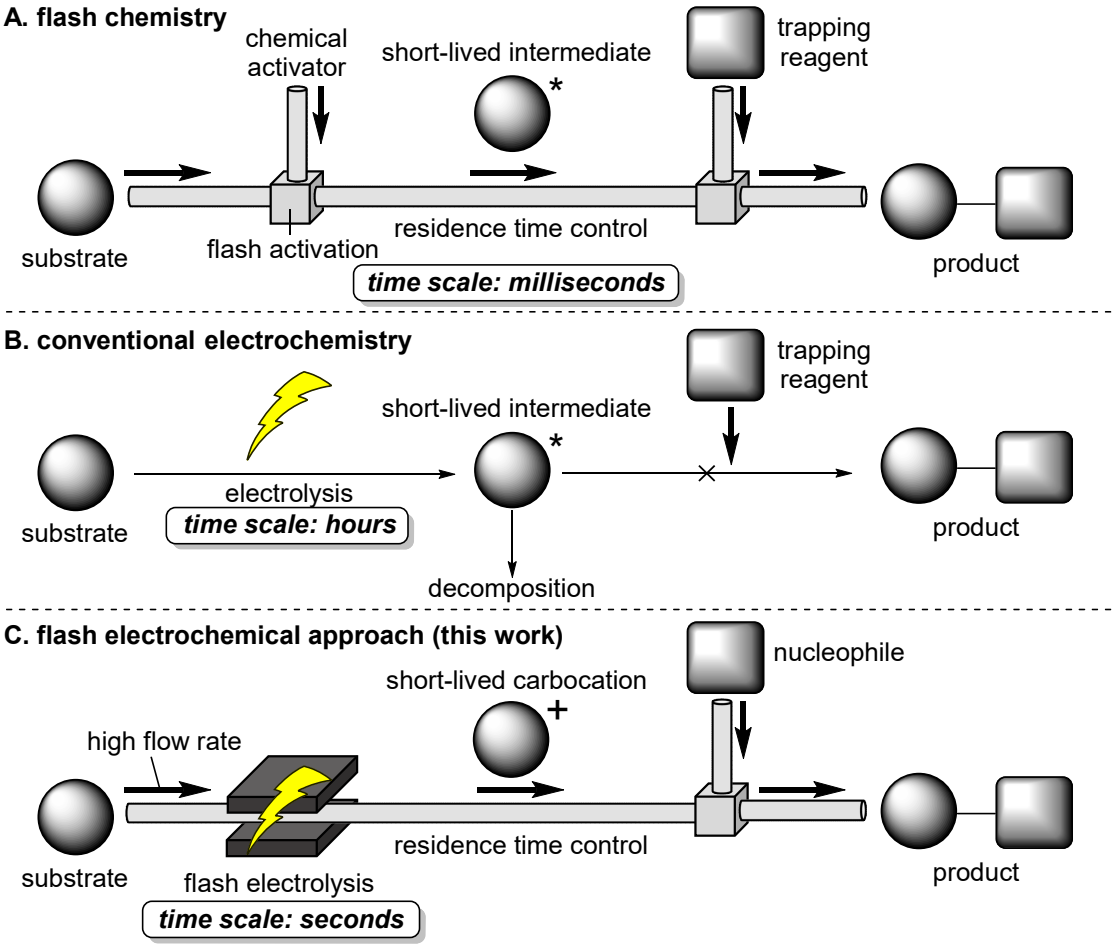


Figure 1. Strategy for utilizing short-lived intermediates.

This chapter describes the development and utilization of a novel flow electrochemical reactor that can perform flash (extremely fast) electrolysis within a few seconds. With the optimization of flow channel and amout of carbon felt anode, the flash generation of short-lived carbocations was achieved in a single passage of reactants through the reactor, enabling the subsequent reaction with nucleophiles before the decomposition of the generated carbocations. Furthermore, multi gram-scale synthesis of a precursor of methylphenidate (Ritalin) was successfully demonstrated by one-hour continuous operation.

Results and Discussion

A flow electrochemical reactor system comprising a divided-type flow electrochemical reactor, microtube reactor, and micromixer was designed to generate and utilize highly

reactive carbocations (Figure 2). The divided-type flow reactor comprised two stainless steel chambers and three stacked polytetrafluoroethylene (PTFE) layers. Thioacetals were selected as substrates for generating oxocarbenium ions and underwent the anodic oxidation in the absence of nucleophiles.[8] A thioacetal solution (**1**, 0.02 M) with a supporting electrolyte (Bu_4NBF_4, 0.3 M) in dichloromethane was introduced by syringe pumping into the anodic chamber equipped with a carbon felt anode. A trifluoromethanesulfonic acid solution (TfOH, 0.05 M) containing the supporting electrolyte (Bu_4NBF_4, 0.3 M) in dichloromethane, which serves as an electrolysis promoter, was also introduced into the cathodic chamber equipped with platinum plate cathode. Constant-current electrolysis was performed at −50 °C, and generated oxocarbenium ion in the anodic chamber was quickly transferred to a microtube reactor **R1**. Then, the resulting solution was quickly mixed with enol silyl ether **2** in a micromixer **M1** and the trapping reaction proceeded in **R2** to give desired product **3**.

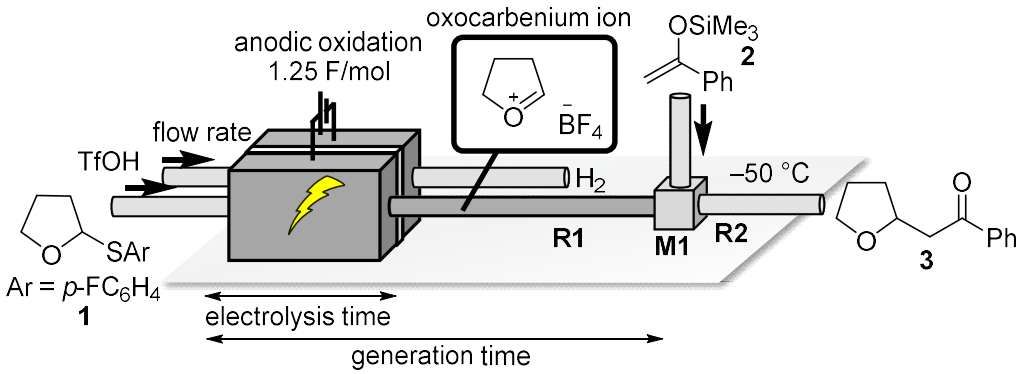
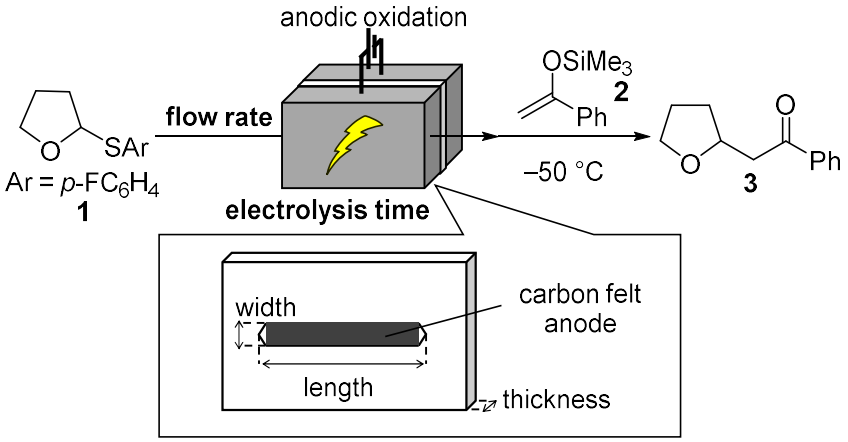


Figure 2. Schematic diagram of electrochemical generation and reaction of oxocarbenium ion in a flow electrochemical reactor system.

To achieve the flash generation of the oxocarbenium ion in a single passage through the reactor, the structure of the anodic flow channel and the quantity of carbon felt anode were optimized (Table 1). In the first trial, with flow channel A at 1 mL/min, moderate yield and conversion were obtained (Table 1, entry 1). At higher flow rates of 2 and 3 mL/min with a higher cell current, further decrease in yield and conversion was observed due to the lower electron transfer efficiency. On the other hand, slight improvement of the conversion and yield was observed with flow channel B (Table 1, entry 2). In addition, flow channel C with another type of structure exhibited a remarkable electrolysis efficiency, even at 3 mL/min, to produce the desired product **3** in 75% yield (Table 1, entry 3). Furthermore, flow channel C with a larger surface area of the carbon felt anode afforded a higher yield (Table 1, entry 4). Notably, quantitative conversions and high yields were maintained even at high flow rates, e.g., 7.0 mL/min, and effective flow electrolysis was accomplished within 4 s.

Table 1. Flash Electrolysis Based on Anodic Flow Channel Optimization.



	entry 1	entry 2	entry 3	entry 4
flow channel	A	B	C	C
width [mm]	2.0	3.0	10	10
length [mm]	42	42	42	42
thickness [mm]	5.0	3.3	1.0	1.0
carbon felt anode [mg]	50	50	50	100
electrode surface area [mm^2]	150	150	180	380
flow rate [mL/min] / electrolysis time [s][a]	yield of **3** (conversion of **1**) [%][b]			
1.0 / 25	51 (74)	76 (89)	69 (>99)	85 (>99)
2.0 / 13	21 (59)	39 (72)	72 (>99)	86 (>99)
3.0 / 8	16 (51)	41 (63)	75 (>99)	87 (>99)
5.0 / 5	-	-	-	90 (>99)
7.0 / 4	-	-	-	93 (>99)
9.0 / 3	-	-	-	88 (95)

[a] Electrolysis time was calculated from the volume of the anodic flow channel and the flow rate.

[b] Determined by GC.

Having accomplished the flash generation, two experiments were conducted to demonstrate the advantage of the present system. First, the stability of the five-membered ring oxocarbenium ion was evaluated by varying the temperature and flow rate to change the generation time. In this chapter, the generation time is the sum of the electrolysis time and the residence time in **R1**. The yields of **3** were plotted against the temperature and the generation time as a contour map with scattered overlays (Figure 3). The map revealed that the yields depend significantly on the temperature and the generation time. The reaction at −25 °C, or lower, afforded the coupling product in high yields, indicating that the

intermediate is stable at such low temperatures. Notably, although the yields decreased markedly at 0 ℃ and 25 ℃ due to the instability of the intermediate, the desired product was obtained in 82% yield in a shorter generation time (4.6 s). The temperature–generation time profile determined in this study is effective in unveiling the lifetime of the unstable carbocations. Moreover, the present system allowed precise control of the temperature and the generation time, achieving the flash electrochemical generation of short-lived carbocations, followed by a nucleophilic trapping reaction at higher temperatures, e.g., 0 ℃, before the decomposition of intermediates.

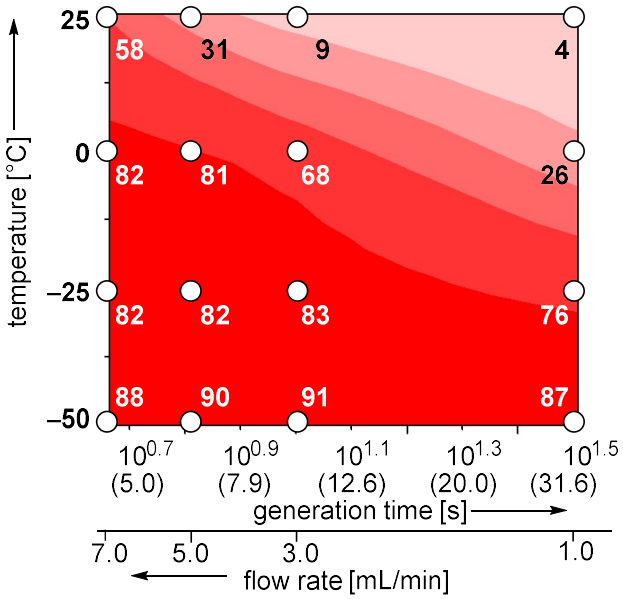
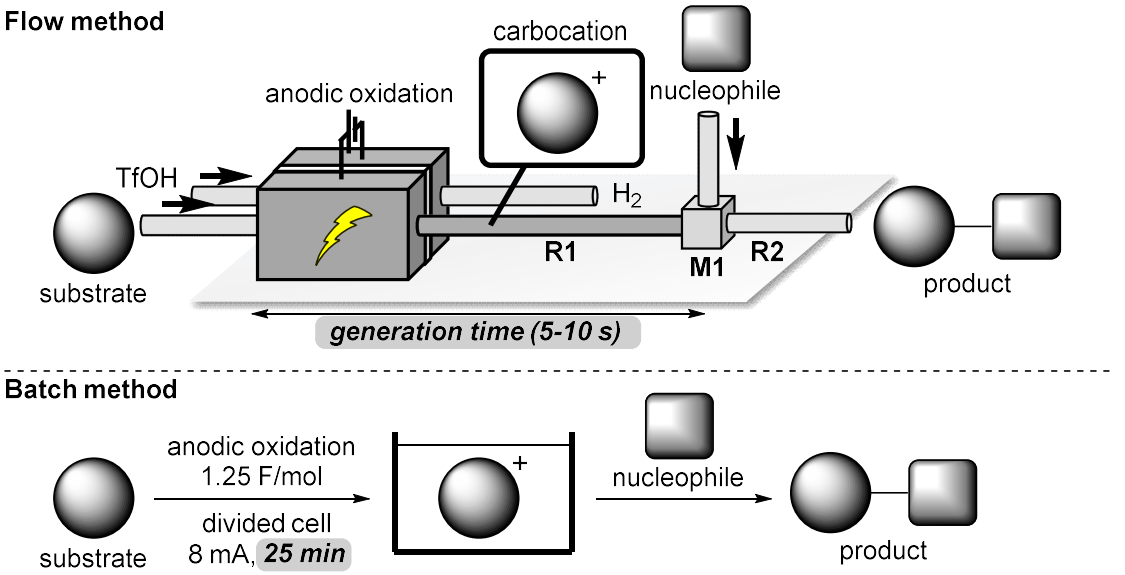
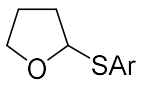
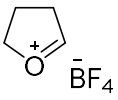
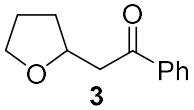
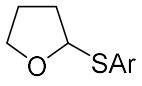
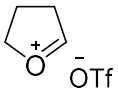
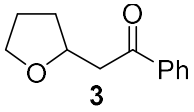
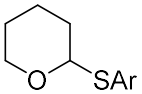
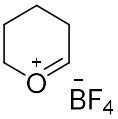
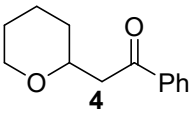
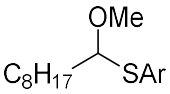
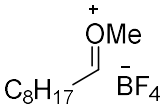
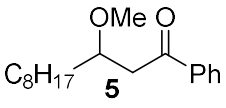
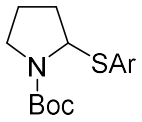
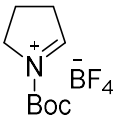
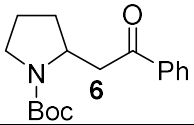


Figure 3. Temperature–generation time map on the yields of **3**.

Second, a comparison between the present flow method and the conventional batch method[9] was performed (Table 2). In the flow system, cyclic and linear oxocarbenium ions were successfully generated and trapped by **2**, providing the corresponding coupling products **3**-**5** in good yields (Table 2, entries 1-4, flow). Moreover, *N*-acyliminium ion bearing the *tert*-butoxycarbonyl (Boc) group which cleaves easily by the undesired electrogenerated acid[10] could be reacted to obtain desired product (Table 2, entry 5, flow). On the other hand, the conventional batch method resulted in much lower yields due to the decomposition during a longer electrolysis process (Table 2, entries 1-5, batch). These results clearly show that the present flow approach is more advantageous for utilizing various short-lived carbocations than conventional batch method.

Table 2. Comparison of Developed Flow Method and Conventional Batch Method.



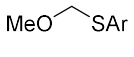
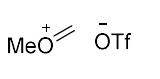
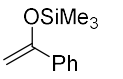
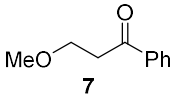
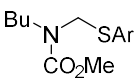
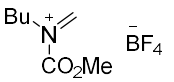
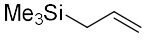
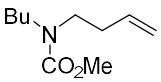
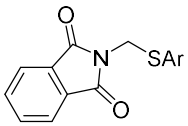
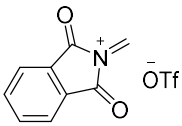
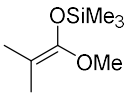
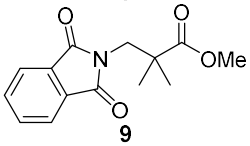
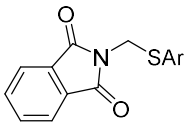
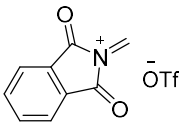
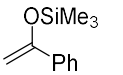
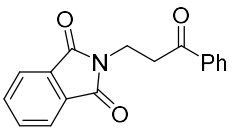
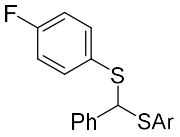
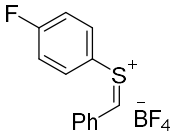
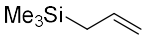
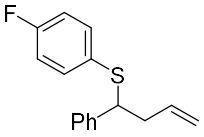
entry	substrate[a]	temperature [°C]	carbocation	product	yield [%][b] batch[c]	yield [%][b] flow[d]
1		0		 **3**	2	82
2		–75		 **3**	17	87[e]
3		–50		 **4**	4[f]	59[g]
4		0		 **5**	4	69
5		0		 **6**	trace	89

[a] Ar = *p*-FC_6H_4. [b] Determined by GC. [c] Batch conditions: H-type divided cell, substrate (0.1 mmol), current = 8 mA, electricity = 1.25 F/mol, electrolysis time = 25 min. [d] Generation time = 5 s, [e] Generation time = 10 s. [f] Determined by ^{1}H NMR. [g] Yield of the isolated compound.

Encouraged by these results, the scope of unstable carbocations was explored (Table 3). Alkoxymethyl triflate having no donating alkyl substituent on the cationic carbon was well converted to corresponding β-alkoxy ketone **7** in 80% yield (Table 3, entry 1). The employment of primary *N*-acyliminium ions was also successful, linear α-amino sulfide

was rapidly oxidized and reacted with allyltrimethylsilane, giving allylated product **8** in quantitative yield (Table 3, entry 2). Additionally, a highly unstable phthalimidomethyl triflate bearing two electron withdrawing carbonyl groups could be trapped by ketene silyl acetal and enol silyl ether and transformed to β-amino ketone derivatives **9** and **10** in 88% and 63% yield respectively (Table 3, entries 3 and 4). Furthermore, thionium ions could be generated and utilized for the reaction with nucleophiles to obtain corresponding product **11** in excellent yield (Table 3, entry 5).

Table 3. Reaction of Short-lived Carbocations with Carbon Nucleophiles in the Flow Electrochemical Reactor System.

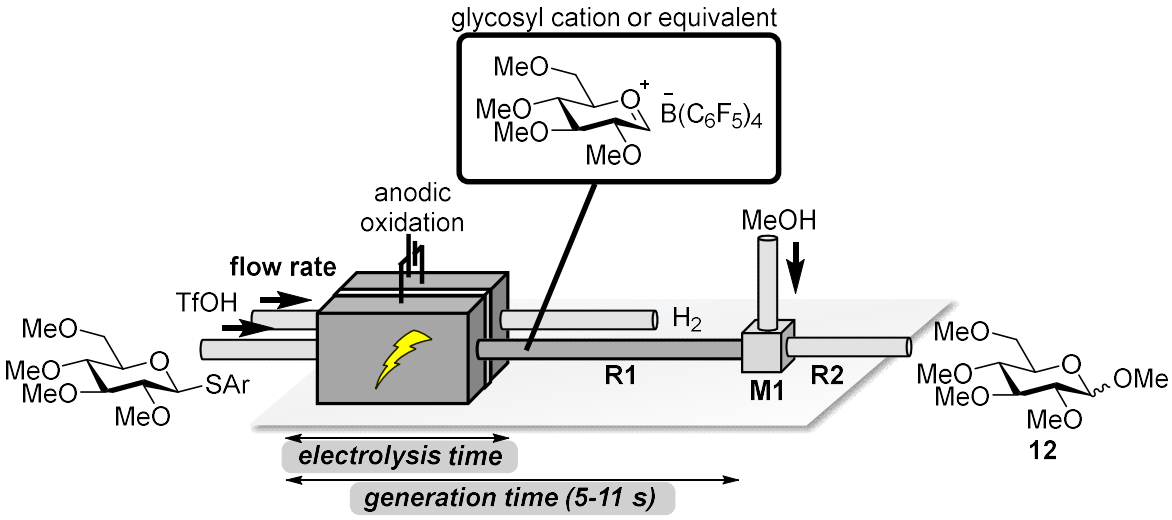
entry	substrate[a]	temperature [°C]	carbocation	nucleophile	product	yield[b]
1		–50			 **7**	80%
2		0			 **8**	quant.[c]
3		–50			 **9**	88%
4		–50			 **10**	63%
5		–50			 **11**	92%

[a] Ar = *p*-FC_6H_4, [b] Yield of the isolated compounds.

Next, generation and utilization of glycosyl cations which are regarded as being considerably more unstable than oxocarbenium ions was examined. It has been previously reported that the use of $Bu_4NB(C_6F_5)_4$ as a supporting electrolyte and counter anion donor enables the electrochemical generation of unstable glycosyl cations.[11] However, because the lifetime of the intermediate is too short to accumulate in batch even at –78 °C, an indirect activation strategy should be used in conventional method. Even for such intermediates, it was confirmed that the present method was also effective (Table 4). The flash electrolysis of tetra-*O*-methyl thioglucoside and immediate trapping of methanol was carried out to obtain desired *O*-glycoside **12** in good yields (Table 4, entry 5). The scope of

this methodology to the glycosylation reaction was investigated (Table 5). The flash electrolysis of tetra-*O*-methyl thioglucoside and immediate trapping with glycosyl doners gave the desired *O*- and *C*-glycosides **13** and **14** in good yields (Table 5, entries 1 and 2). Moreover, thioribofulanoside and thioglucosamine also served as good glycosyl donors to obtain the desired *O*-glycosides **15** and **16** in moderate yield (Table 5, entries 3 and 4).

Table 4. Flash Generation of Glycosyl Cation in the flow electrochemical reactor system.

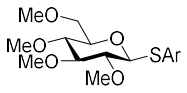
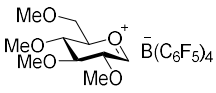
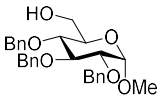
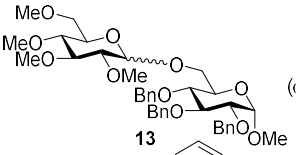
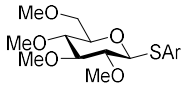
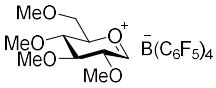
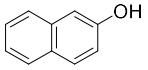
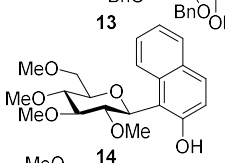
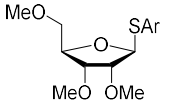
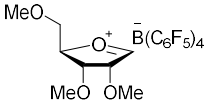
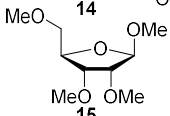
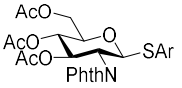
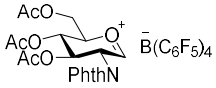
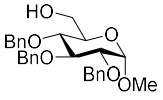
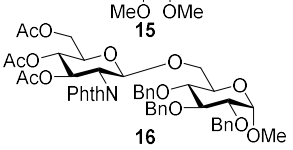


entry	temperature [°C]	flow rate [mL/min]	electrolysis time [s]	generation time [s]	yield of **12** (α/β) [%][b]
1	–50	batch	1500	1500	41 (58/42)
2	–50	3.0	8	11	60 (66/34)
3	–50	5.0	5	7	65 (57/43)
4	–50	7.0	4	5	73 (60/40)
5	–75	7.0	4	5	78 (65/35)[c]

[a] Flow conditions: electricity = 1.25 F/mol, additional stirring = rt, 30 min. [b] Determined by ^{1}H NMR.

[c] Yield of the isolated compound.

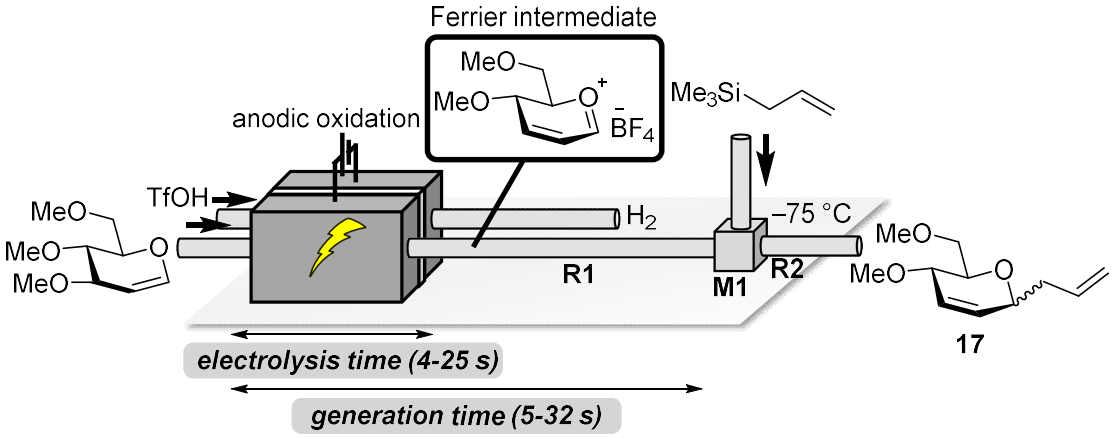
Table 5. Glycosylation of Short-lived Glycosyl Cations in the Flow Electrochemical Reactor System.

entry	substrate[a]	temperature [°C]	carbocation	nucleophile	product	yield[b]
1		–75			 **13**	84% (α/β = 66/34)
2		–75[d]			 **14**	79% (β only)
3		–75		MeOH	 **15**	60% (β only)
4		–75			 **16**	57% (β only)

[a] Ar = *p*-FC_6H_4, [b] Yield of the isolated compound. [c] Determined by GC analysis. [d] Reaction with nucleophile was carried out at 0 °C.

Furthermore, this flash electrolysis approach offers unique access to the Ferrier intermediates. In carbohydrate chemistry, the Ferrier intermediates are unstable allylic oxocarbenium ions that play an important role in the construction of 2,3-unsaturated glycosides.[12] Although reactions using several chemical oxidants such as 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) or ceric (IV) ammonium nitrate (CAN) have been reported to promote the Ferrier rearrangement,[13] there are no reports on direct electrooxidative generation of the Ferrier intermediates from glycals. The electrochemical single-electron oxidation of tri-*O*-methyl-D-glycal followed by the reaction with allyltrimethylsilane using a batch electrochemical reactor in a Bu_4NBF_4/CH_2Cl_2 system gave a low yield, presumably because slow electrolysis caused undesired dimerization and oligomerization (Table 6, entry 1). In the flash electrolysis approach, the decrease in the electrolysis time with the increase in the flow rate (generation time = 32 s) resulted in a significant improvement in the yields and suppression of the undesired dimerization and oligomerization (Table 6, entries 2-5). Moreover, applying the shortest generation time (5 s) enabled the desired *C*-glycoside **17** formation in 71% yield (Table 6, entry 7).

Table 6. Flash Generation of the Ferrier Intermediate in the Flow Electrochemical Reactor System.

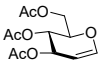
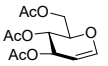
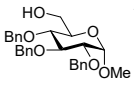
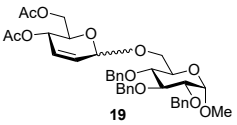
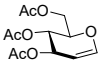
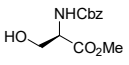
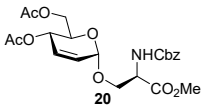
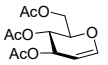
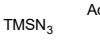
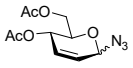
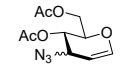
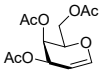
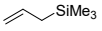
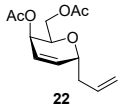
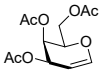
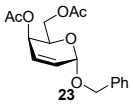


entry	Electrolysis time [s]	Residence time in **R1** [s]	Generation time [s]	Yield of **17** [%][a]
1	1500 (batch)	-	-	11 (α/β = 91/9)
2	25	7	32	32 (α/β = 94/6)
3	8	24	32	41 (α/β = 93/7)
4	5	27	32	56 (α/β = 93/7)
5	4	28	32	60 (α/β = 92/8)
6	4	7	11	66 (α/β = 92/8)
7	4	1	5	71 (α/β = 95/5)[b]

[a] Determined by GC analysis. [b] Yield of the isolated compound.

Under the optimized condition, the scope of this methodology was examined (Table 7). The reactions of acetyl protected glycals with *O*-nucleophiles, trimethylsilyl azide and allytrimethylsilane proceeded smoothly to afford the corresponding 2,3-unsaturated glycosides **18**-**23**. Notably, high α selectivity of the products was observed in a series of studies, which is consistent with the spectroscopic studies of the Ferrier intermediates in a super acidic media.[14]

Table 7. Electrochemical Synthesis of 2,3-Unsaturated Glycosides from Glycals.

entry	substrate	nucleophile	product[b]
1			 **18** 74% (α/β = 94/6)
2			 **19** 76% (α/β = 81/19)
3			 **20** 63% (α only)
4[c]			 **21** 33% (α/β = 98/2)  **21'** 19% (α/β = 42/58)
5			 **22** 64% (α only)
6			 **23** 54% (α only)

[a] General conditions: electricity = 1.25 F/mol, electrolysis temperature = –75 °C, electrolysis time = 4 s, generation time = 5 s, additional stirring = rt, 30 min. [b] Yield of the isolated compounds. [c] Additional stirring = –30 °C, 30 min.

Finally, a feasibility study of the proposed flow system for continuous operation was carried out through the synthesis of a precursor of methylphenidate (Ritalin),[15] a potent psychotropic medicine (Figure 4).[16] During the continuous operation for 60 min, the temperature of the Peltier cooling system could be precisely controlled at –50 °C, enabling the steady generation of the six-membered ring *N*-acyliminium ion and demonstrating the robustness of the system. After the operation, *N*-Boc methylphenidate **24** was obtained (2.3 g, 83% yield) and the obtained product should be led to Ritalin by simple reported deprotection and resolution procedure.[17] The entire reaction, including anodic oxidation in a single passage of the reactant through the cell and trapping reaction of the generated carbocation with nucleophile, could be accomplished within 19 s, allowing quick access to the pharmaceutical precursor on demand.

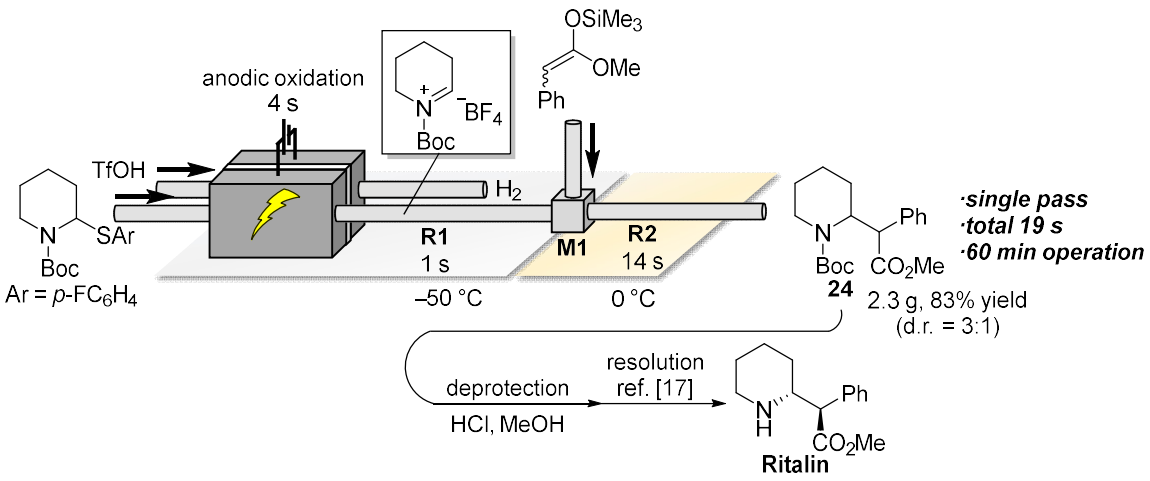


Figure 4. Continuous and rapid production of *N*-Boc methylphenidate.

Conclusion

A novel flow electrochemical reactor system that can accomplish electrolysis within a few seconds was developed, which enabled the flash electrooxidative generation of short-lived carbocations followed by a nucleophilic trapping reaction before their decomposition. Furthermore, the present system is applicable to continuous operation, achieving the rapid production of a pharmaceutical precursor, *N*-Boc methylphenidate on demand. The flow electrochemical reactor system described herein opens a new aspect of both electrochemistry and flow chemistry.

Experimental Section

General.

^{1}H and ^{13}C NMR spectra were recorded on Varian MERCURY plus-400 (^{1}H: 400 MHz, ^{13}C: 100 MHz). Chemical shifts were recorded using TMS (0.0 ppm) or $CDCl_3$ (7.26 ppm) signals as an internal standard for ^{1}H NMR, and methin signal of $CDCl_3$ for ^{13}C NMR (77.0 ppm) unless otherwise noted. NMR yields were calculated by ^{1}H NMR analyses with 10 seconds relaxation delay using 1,1,2,2-tetrachloroethane as an internal standard. GC analysis was performed on a Shimadzu GC-2014 gas chromatograph equipped with a flame ionization detector using a fused silica capillary column (Rtx-200; 30 m × 0.25 mm × 0.25 μm). GC yields were calculated by GC analysis using calibration lines derived from

commercial or isolated compounds with the internal standards. Mass spectra were recorded on Thermo Fisher Scientific EXACTIVE plus (ESI and APCI) or JEOL JMS-700 (EI). Infrared absorption (IR) spectra were recorded on a Mettler Toledo ReactIR 15 as a chloroform ($CHCl_3$) solution and selected absorption maxima (ν_{max}) were reported in wavenumbers (cm^{-1}). Melting points were recorded on a Yanaco micro melting point apparatus and reported in degrees Celsius (°C). Flash chromatography was carried out on a silica gel (Kanto Chem. Co., Silica Gel N, spherical, neutral, 40–100 μm). Merck pre-coated silica gel F_{254} plates (thickness 0.25 mm) were used for TLC analyses. All solution preparations and reactions were carried out in a flame-dried glassware under argon atmosphere using dehydrated solvent unless otherwise noted. Gel permeation chromatography (GPC) was carried out on a Japan Analytical Industry LC-9201 equipped with JAIGEL-1H and 2H using $CHCl_3$ as eluent. Stainless steel (SUS304) T-shaped micromixer (ϕ = 500 μm) was manufactured by Sanko Seiki Co., Inc. Stainless steel (SUS316) microtube reactors (ϕ = 500 and 1000 μm) were purchased from GL Sciences. PTFE tube (ϕ = 1000 μm) was purchased from ISIS Co., Ltd. The syringe pumps (Harvard Model PHD ULTRA) equipped with gastight syringes (purchased from SGE) were used for introduction of the solutions into the microreactor systems via stainless steel fittings (GL Sciences, 1/16 OUW). The plunger pumps (Shimadzu, LC-20AD) were used for continuous synthesis instead of the syringe pumps. The divided electrochemical flow reactor and Peltier cooling system were purchased from DFC Co., Ltd. Carbon felt for anode (GF-20-P7) was purchased from Nippon Carbon Co., Ltd. and dried at 300 °C/1 mm Hg for 3 hours before use. Pt plate for cathode was purchased from Nilaco Co., Ltd. Glass filter (Whatman, GF/A) and PTFE membrane (Millipore, pore size is 0.2 μm) were purchased from commercial suppliers. A Kikusui PMC350-0.2A was used as a direct current power supply for the electrolysis. Reagents were purchased from commercial suppliers and used without further purification unless otherwise noted. Bu_4NBF_4 and Bu_4NOTf were purchased from Sigma-Aldrich and dried at 80 °C/1 mmHg over 12 hours before use. $Bu_4NB(C_6F_5)_4$ was synthesized according to the literature procedure[11(a)] and dried at 80 °C/1 mmHg over 12 h. 2-(4-Fluorophenylthio)-tetrahydropyran,[11(a)] 1-methoxy-1-(4-fluorophenylthio)nonane,[8(b)] 4-fluorophenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside,[18] methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside,[19] 4-fluorophenyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside,[20] 1-fluoro-4-((methoxymethyl)thio)benzene,[21] bis(4-fluorophenyl) disulfide,[22] 1-chloromethylthio-4 -fluorobenzene,[23] tri-*O*-methyl-D-glucal,[24] phenyl ketene methyl(trimethylsilyl)acetal,[25] *S*,*S'*-bis(*p*-fluorophenyl)benz-aldehydedithioacetal[26] were synthesized according to the reported procedures.

Preparation of 2-((4-fluorophenyl)thio)tetrahydrofuran 1.

To a mixture of 2,3-dihydrofuran (5.6 g, 79.6 mmol) and 4-fluorothiophenol (6.4 g, 49.6 mmol) in THF (100 mL), was added $BF_3 \cdot OEt_2$ (7.3 g, 51.8 mmol) at 0 ℃. The reaction mixture was stirred for 12 h at room temperature, then sat. $NaHCO_3$ aq. was added. After separation and extraction by Et_2O, organic layer was dried over $MgSO_4$ and the solvent was evaporated under reduced pressure. The residue was purified by flash chromatography (hexane/ethyl acetate = 4/1) to give **1** in 65% yield (6.4 g, 32.2 mmol) ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.83-2.06 (m, 3H), 2.30-2.40 (m, 1H), 3.92-4.05 (m, 2H), 5.52-5.56 (m, 1H), 6.97-7.03 (m, 2H), 7.46-7.52 (m, 2H). The NMR spectrum is in good agreement with that in the literature.[27]

Preparation of *tert*-butyl 2-((4-fluorophenyl)thio)pyrrolidine-1-carboxylate.

To a solution of 1-*tert*-butoxycarbonylpyrrolidine (3.63 g, 21.2 mmol) in THF (100 mL), was added *sec*-BuLi (1.06 M in cyclohexane, 25 mL, 26.5 mmol) dropwise at −78 ℃. The reaction mixture was stirred at the same temperature for 1 h. To the reaction mixture, was added a solution of bis(4-fluorophenyl) disulfide (7.16 g, 28.2 mmol) in THF (25 mL) dropwise at −78 ℃. Then the mixture was warmed to room temperature and stirred overnight. The reaction mixture was treated with sat. NH_4Cl aq. and extracted with Et_2O. The combined organic phase was dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by flash chromatography on silica gel (hexane/ethyl acetate 30:1) and subsequent recrystallization from hexane to afford the title compound as a colorless solid in 19% yield (1.22 g, 4.1 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.28-1.50 (m, 9H), 1.85-2.20 (m, 4H), 3.20-3.47 (m, 2H), 5.18-5.36 (m, 1H), 6.94-7.05 (m, 2H), 7.41-7.56 (m, 2H). The NMR spectrum is in good agreement with that in the literature.[28]

Preparation of methyl butyl(((4-fluorophenyl)thio)methyl)carbamate.

To a solution of *N*-(methoxycarbonyl)butylamine (3.92 g, 29.9 mmol) in DMF (50 mL), was slowly added a sodium hydride NaH (60 wt% dispersion in paraffin liquid, 1.44 g, 36.1 mmol) at 0 ℃. The reaction mixture was stirred at 60 ℃ for 2 h. Then the mixture was cooled at 0 ℃, and 1-chloromethylthio-4-fluorobenzene (6.40 g, 36.3 mmol) was added. After stirring at 50 °C overnight, the mixture was poured into water. After extraction with Et_2O, the combined organic phase was dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by flash chromatography (hexane/ethyl acetate 10/1) to give the title compound as a yellow oil in 13% yield (1.03 g, 3.8 mmol). TLC: Rf = 0.27 (hexane/ethyl acetate = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85-0.92 (m, 3H), 1.19-1.33 (m, 2H), 1.40-1.54 (m, 2H), 3.22-3.30 (m, 1H) 3.34 (s, 3H), 4.64 (s) and

4.75 (s) (total 2H, two rotamer), 3.61 (s, 1H), 6.98 (t, *J* = 8.0 Hz, 2H), 7.41-7.48 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 13.7. 19.9, 29.6, 30.1, 45.4, 45.6, 52.3, 52.7, 53.6, 115.9 (d, *J* = 21.6 Hz), 128.7 (d, *J* = 30.4 Hz), 134. 9 (d, *J* = 7.2 Hz), 136.4 (d, *J* = 8.0 Hz), 156.0, 156.5, 161.3, 161.6, 163.8, 164.0; HRMS (ESI) calcd for $C_{13}H_{18}FNO_2SNa$ [M+Na^+]: 294.0934, found 294.0937; IR ($CHCl_3$ solution) ν_{max}: 1700 cm^{-1}.

Preparation of 2-(((4-fluorophenyl)thio)methyl)isoindoline-1,3-dione.

To a solution of phthalimide potassium salt (2.04 g, 11.0 mmol) in DMF (20 mL), was added 1-chloromethylthio-4-fluorobenzene (1.77 g, 10.0 mmol) at room temperature. The reaction mixture was stirred at 60 ℃ overnight. Then H_2O and CH_2Cl_2 were added to the reaction mixture. After extraction with CH_2Cl_2, the combined organic phase was dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was recrystallized from hexane and CH_2Cl_2 to give the title compound as a white solid in 73% yield (2.11 g, 7.3 mmol). TLC: Rf = 0.42 (hexane/ethyl acetate = 3/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.98 (s, 2H), 6.97 (t, *J* = 8.8 Hz, 2H), 7.47 (dd, *J* = 5.3 Hz, *J* = 8.8 Hz), 7.70-7.75 (m, 2H), 7.80-7.85 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 42.9, 116.2 (d, *J* = 21.8 Hz), 123.4, 128.0 (d, *J* = 3.2 Hz), 131.8, 134.3, 135.6 (d, *J* = 8.3 Hz), 162.9 (d, *J* = 246.8 Hz), 166.8; HRMS (EI) calcd for $C_{15}H_{10}FNO_2S$ [$M^{+\cdot}$]: 287.0411, found 287.0413; IR ($CHCl_3$ solution) ν_{max}: 1722 cm^{-1}.

Preparation of 4-fluorophenyl 2,3,4,6-tetra-*O*-methyl-1-thio-β-D-glucopyranoside.

To a solution of 4-Fluorophenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (6.87 g, 15 mmol) in MeOH (30 mL), was added a sodium methoxide (28 wt% in MeOH, 2.0 mL) at room temperature. The reaction mixture was stirred at room temperature for 12 h. After stirring, solvent was evaporated under reduced pressure to give a white solid. The white solid was redissolved in DMF (150 mL) and cooled to 0 ℃. To the mixture, was added NaH (60 wt% dispersion in paraffin liquid, 3.6 g, 90 mmol) at the same temperature. After stirring for 30 min, methyl iodide (12.8 g, 90 mmol) was added at 0 ℃. Then, the reaction mixture was stirred at room temperature for 8 h. The reaction was quenched by adding sat. NH_4Cl aq. After extracting with ethyl acetate, the combined organic layer was washed with brine and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by flash chromatography (hexane/ethyl acetate 5/1) to give the title compound as a white solid in 84% yield (4.3 g, 12.4 mmol). TLC: Rf = 0.27 (hexane/ethyl acetate = 3/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.00 (t, *J* = 8.0 Hz, 3H), 3.21-3.23 (m, 2H), 3.23-3.27 (m, 1H), 3.39 (s, 3H), 3.52 (s, 3H), 3.53-3.57 (m, 1H), 3.60 (s,3H), 3.61-3.64 (m, 1H), 3.64 (s, 3H), 4.38 (d, *J* = 9.6 Hz, 1H), 6.96-7.02 (m, 2H), 7.51-7.56 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 59.3, 60.5, 60.8, 61.0, 71.3, 78.7, 79.3, 82.5, 87.7, 88.6, 115.8 (d, *J* =

21.6 Hz), 128.6 (d, *J* = 3.6 Hz), 134.6 (d, *J* = 8.0 Hz), 162.6 (d, *J* = 247.7 Hz); HRMS (ESI) calcd for $C_{16}H_{23}FO_5SNa$ [M+Na^+]:369.1142, found 369.1147; Melting point: 54-56 ℃.

Preparation of 4-fluorophenyl 2,3,5-tri-*O*-methyl-β-D-thioribofuranoside.

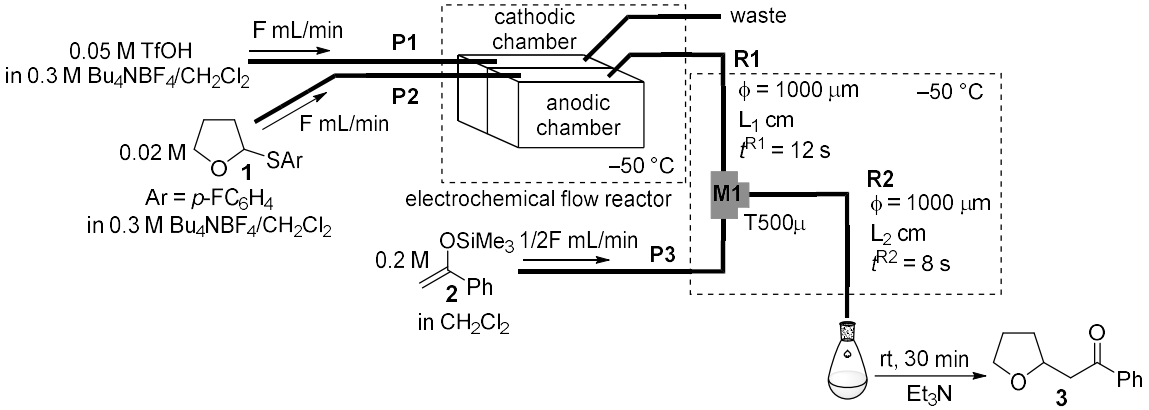
To a solution of tetra-*O*-acetyl-β-D-ribofuranose (9.55g, 30 mmol) and 4-fluorothiophenol (4.32 g, 34mmol) in CH_2Cl_2 (50 mL), was added a $BF_3{\cdot}OEt_2$ (4.75 g, 33 mmol) at 0 ℃. The reaction mixture was stirred at room temperature for 12 h. The reaction was quenched with sat. $NaHCO_3$ aq. and extracted with ethyl acetate. The combined organic phase was dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by flash chromatography on silica gel (hexane/ethyl acetate = 2/1) to give 4-fluorophenyl 2,3,5-tri-*O*-acetyl-D-thioriboside as a yellow oil in 91% (10.6 g, 27.4 mmol). To a solution of 4-Fluorophenyl 2,3,5-tri-*O*-acetyl-D-thioriboside (5.80 g, 15 mmol) in MeOH (25 mL), was added K_2CO_3 (2.19 g, 15.8 mmol) at room temperature. The reaction mixture was stirred at room temperature for 12 h. The resulting heterogeneous mixture was filtrated, and the filtrate was evaporated under reduced pressure to give a white solid. To a solution of the white solid in DMF (50 mL), was added NaH (60 wt% dispersion in paraffin liquid, 1.64 g, 42 mmol) at 0 ℃. The mixture was stirred at the same temperature for 1 h. Then, methyl iodide (5.81 g, 41 mmol) was slowly added at 0 ℃ and the reaction mixture was stirred at room temperature for 12 h. The reaction was quenched by H_2O and extracting with ethyl acetate. The combined organic phase was washed with brine, dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by flash chromatography on silica gel (hexane/ethyl acetate = 2/1) to give the title compound as a pale yellow oil in 47% yield (2.1 g, 7.0 mmol). TLC: Rf = 0.23 (hexane/ethyl acetate = 2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.38 (s, 3H), 3.42 (s, 3H), 3.47 (s, 3H), 3.49 (d, *J* = 4.8 Hz, 2H), 3.75-3.78 (m, 2H), 4.13-4.17 (m, 1H), 5.26 (d, *J* = 3.2 Hz, 1H), 6.98-7.04 (m, 2H), 7.49-7.54 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 58.1, 58.3, 59.4, 73.2, 79.7, 81.3, 82.8, 88.5, 116.0 (d, *J* = 21.8 Hz), 128.4, 134.9 (d, *J* = 8.3 Hz), 162.7 (d, *J* = 246.0 Hz); HRMS (ESI) calcd for $C_{14}H_{19}FO_4SNa$ [M+Na^+]: 325.0880, found 325.0886.

Preparation of *tert*-butyl 2-((4-fluorophenyl)thio)piperidine-1-carboxylate.

To a solution of 1-(*tert*-butoxycarbonyl)piperidine (1.92 g, 10.4 mmol) in Et_2O (18 mL) , was added TMEDA (1.95 mL, 1.52 g, 13.1 mmol) and *sec*-BuLi (1.22 M in cyclohexane, 10.5 mL, 12.8 mmol) at −78 ℃ in this order. The reaction mixture was slowly warmed to −40 ℃ and stirred for 30 min. Then the reaction mixture was cooled to −78 ℃ again. To the mixture was added a bis(4-fluorophenyl) disulfide (5.2 g, 20.4 mmol) at −78 ℃. Then the mixture was slowly warmed to room temperature and stirred overnight. The reaction was quenched with H_2O, extracted with Et_2O. The combined organic phase was dried over

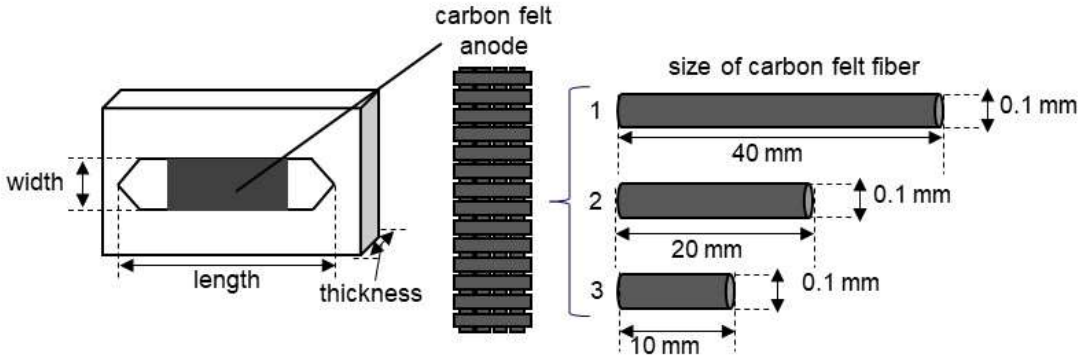
$MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by flash chromatography on silica gel (hexane/ethyl acetate 30/1) and subsequent recrystallization from hexane to give the title compound as a white solid in 47% yield (1.52 g, 4.9 mmol). TLC: Rf = 0.07 (hexane/ethyl acetate = 30/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.16 (br s) and 1.29 (br s) (total 9H), 1.35-1.55 (br s, 1H) 1.60-2.02 (m, 5H), 3.23-3.34 (m, 1H), 3.77-4.13 (m, 1H) 5.71 (s) and 5.98 (s) (total 1H, two rotamer), 6.90-7.03 (m, 2H), 7.40-7.52 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.7, 25.4, 27.9, 30.1, 31.0, 37.9, 39.2, 62.2, 64.3, 79.8, 115.9 (d, J = 20.8 Hz), 128.6 (d, J = 52.3 Hz), 136.9 (d, J = 61.5 Hz), 153.7, 163.0 (d, J = 246.5); HRMS (ESI) calcd for $C_{16}H_{22}NO_2SNa$ [M+Na$^+$]: 334.1247, found 334.1252; IR ($CHCl_3$ solution) ν_{max}: 1686 cm^{-1}; MP: 55-57 °C.

Optimization of Anodic Flow Channel.



An electrochemical flow reactor system consisting of a divided electrochemical flow reactor, a T-shaped micromixer (**M1**), two microtube reactors (**R1** and **R2**), and three pre-cooling units (**P1** (L = 200 cm), **P2** (200 cm) and **P3** (100 cm)) was used. The electrochemical reactor was cooled at −50 °C by a Peltier cooling system, and the flow microreactor system composed with **P1**, **P2**, **P3**, **R1**, **R2** and **M1** was cooled in acetone baths at −50 °C. During the operation, the amount of solution was monitored by sampling the solution and adjusted by changing diameter and length of tube reactor connected to the cathodic chamber. For the optimization of the anodic flow channel, flow channels A-C were used (Table S1). And the shape of PTFE plate for cathodic flow channel was same as the flow channel C.

Table S1. Details of Anodic Flow Channel and Carbon Felt Anode.



	flow channel	A	B	C	C
flow set up	thickness [mm]	5.0	3.0	1.0	1.0
	width [mm]	2.0	3.3	10	10
	length [mm]	42	42	42	42
	carbon felt [mg]	50	50	50	100
number of carbon felt fibers in the anode	carbon felt fiber 1	12	12	-	10
	carbon felt fiber 2	-	-	10	-
	carbon felt fiber 3	-	-	40	80
calculated anode surface area [mm^2]		150	150	180	380

A solution of Trifluoromethanesulfonic Acid (TfOH) (0.05 M in Bu_4NBF_4/CH_2Cl_2, flow rate: F mL/min) was introduced to the cathodic chamber through **P1**. A solution of 2-((4-Fluorophenyl)thio)tetrahydrofuran **1** (0.02 M in Bu_4NBF_4/CH_2Cl_2, flow rate: F mL/min) was introduced to the anodic chamber through **P2**. The constant current electrolysis was carried out at −50 °C. Current value was set to consume 1.25 F/mol of electricity. The resulting solution from anodic chamber was passed through **R1** (L_1 cm, residence time t^{R1} = 12 s) and introduced to **M1** (ϕ = 500 μm), where a solution of 1-phenyl-1-(trimethylsilyloxy)ethylene **2** (0.2 M in CH_2Cl_2) was also introduced (flow rate: 1/2F mL/min). The mixed solution was passed through **R2** (L_2 cm, residence time t^{R2} = 8 s). After a steady state was reached, the product solution was collected and stirred at room temperature for 30 min. After addition of triethylamine Et_3N (1 mL) to the crude, the solvent was removed under reduced pressure. To the crude product, Et_2O and *n*-pentadecane were added, and the mixture was analyzed by GC. The results are summarized in Table S2.

Table S2. Optimization of Anodic Flow Channel.

entry	anodic flow channel	carbon felt [mg]	flow rate F [mL/min]	current [mA]	current density [mA/cm^2] [a]	electrolysis time [s] [b]	L_1 [cm]	L_2 [cm]	conversion of **1** [%]	yield of **3** [%]
1	A	50	1.0	40	50	25.2	25	25	74	51
2	A	50	2.0	80	100	12.6	50	50	59	21
3	A	50	3.0	120	150	8.4	75	75	51	16
4	B	50	1.0	40	30	25.2	25	25	89	76
5	B	50	2.0	80	60	12.6	50	50	72	39
6	B	50	3.0	120	90	8.4	75	75	63	41
7	C	50	1.0	40	20	25.2	25	25	>99	69
8	C	50	2.0	80	40	12.6	50	50	>99	72
9	C	50	3.0	120	60	8.4	75	75	>99	75
10	C	100	1.0	40	10	25.2	25	25	>99	85
11	C	100	2.0	80	20	12.6	50	50	>99	86
12	C	100	3.0	120	30	8.4	75	75	>99	87
13	C	100	5.0	200	50	5.0	125	125	>99	90
14	C	100	7.0	280	70	3.6	175	175	>99	93
15	C	100	9.0	360	90	2.8	225	225	95	88

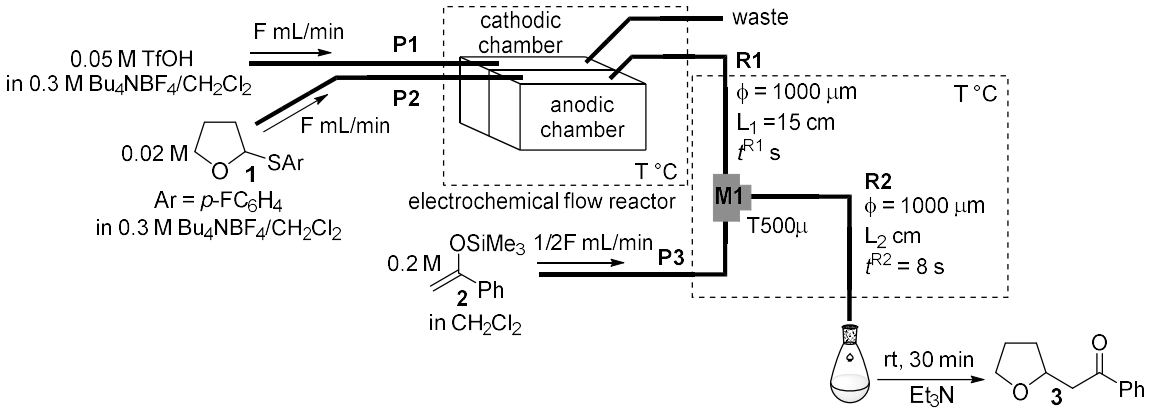
[a] Calculated from the current and the cross section of the anodic channel.

[b] Calculated from the volume of the anodic flow channel and the flow rate.

1-Phenyl-2-(tetrahydro-2-furanyl)ethenone 3.

Electrochemical oxidation (1.25 F/mol) of **1** and subsequent reaction with **2** gave the title compound. The crude was analyzed by GC using pentadecane as an internal standard. GC retention time = 20.9 min; initial oven temperature, 50 °C for 5 min; rate of temperature increase, 10 °C/min; ^{1}H NMR (400 MHz, $CDCl_3$) δ1.54 (m, 1H), 1.93 (m, 2H), 2.20 (m, 1H), 3.06 (dd, J_1 = 6.8 Hz, J_2 = 9.6 Hz, 1H), 3.40 (dd, J_1 = 6.4 Hz, J_2 = 10.0 Hz, 1H), 3.76 (q, J = 7.2 Hz, 1H), 3.90 (q, J = 7.2 Hz, 1H), 4.41 (m, 1H), 7.47 (t, J = 7.2 Hz, 2H), 7.57 (t, J = 7.6 Hz, 1H), 7.94 (d, J = 6.4 Hz, 2H). The NMR spectrum is in good agreement with that in the literature.[29]

Effect of Temperature and Generation Time on the Reaction of Oxocarbenium Ion.



An electrochemical flow reactor system consisting of a divided electrochemical flow reactor, a T-shaped micromixer (**M1**), two microtube reactors (**R1** and **R2**), and three pre-cooling units (**P1** (L = 200 cm), **P2** (200 cm) and **P3** (100 cm)) was used. The electrochemical reactor was cooled at T °C by a Peltier cooling system, and the flow microreactor system composed with **P1**, **P2**, **P3**, **R1**, **R2** and **M1** was cooled in acetone baths at T °C. During the operation, the amount of solution was monitored by sampling the solution and adjusted by changing diameter and length of tube reactor connected to the cathodic chamber. The flow channel C was used for the anodic flow channel and the shape of PTFE plate for cathodic flow channel was same as the flow channel C, and the amount of carbon felt was 100 mg. In the following experiments, the same flow channel condition was used unless otherwise noted. A solution of TfOH (0.05 M in Bu_4NBF_4/CH_2Cl_2, flow rate: F mL/min) was introduced to the cathodic chamber through **P1**. A solution of **1** (0.02 M in Bu_4NBF_4/CH_2Cl_2, flow rate: F mL/min) was introduced to the anodic chamber through **P2**. The constant current electrolysis was carried out at T °C. Current value was set to consume 1.25 F/mol of electricity. The resulting solution from anodic chamber was passed through **R1** (15 cm, residence time t^{R1} s) and introduced to **M1** (ϕ = 500 μm), where a solution of **2** (0.2 M in CH_2Cl_2) was also introduced (flow rate: 1/2F mL/min). The mixed solution was passed through **R2** (L_2 cm, residence time t^{R2} = 8 s). After a steady state was reached, the product solution was collected and stirred at room temperature for 30 min. After addition of Et_3N (1 mL) to the crude, the solvent was removed under reduced pressure. To the crude product, Et_2O and pentadecane were added, and the mixture was analyzed by GC. The results are summarized in Table S3.

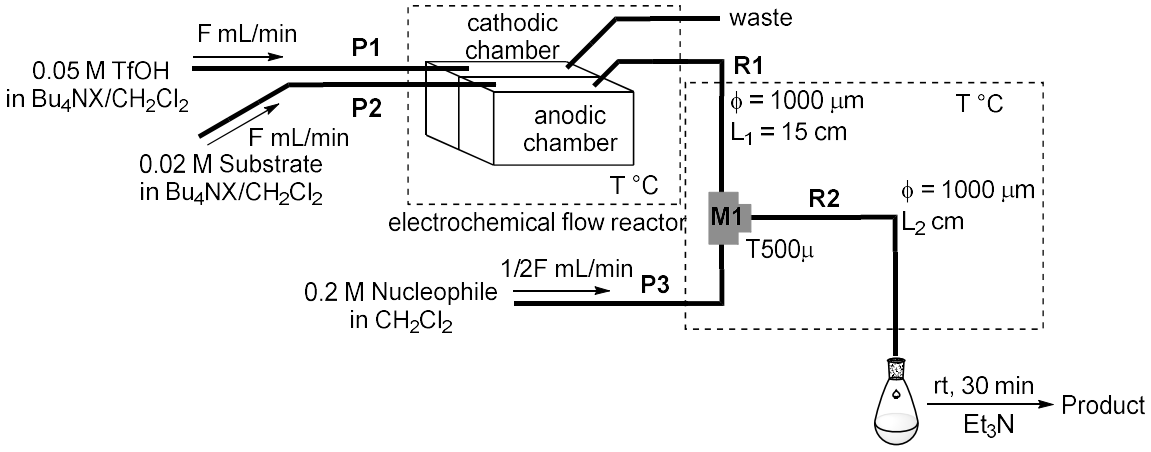
Table S3. Effect of Temperature and Generation Time on the Yield of **3**.

entry	T [°C]	F [mL/min]	current [mA]	electrolysis time [s] [a]	t^{R1} [s]	generation time [s] [b]	L_2 [cm]	yield of **3** [%]
1	25	1.0	40	25.2	7.1	32.3	25	4
2	25	3.0	120	8.4	2.4	10.8	75	9
3	25	5.0	200	5.0	1.4	6.5	125	31
4	25	7.0	280	3.6	1.0	4.6	175	58
5	0	1.0	40	25.2	7.1	32.3	25	26
6	0	3.0	120	8.4	2.4	10.8	75	68
7	0	5.0	200	5.0	1.4	6.5	125	81
8	0	7.0	280	3.6	1.0	4.6	175	82
9	–25	1.0	40	25.2	7.1	32.3	25	76
10	–25	3.0	120	8.4	2.4	10.8	75	83
11	–25	5.0	200	5.0	1.4	6.5	125	82
12	–25	7.0	280	3.6	1.0	4.6	175	82
13	–50	1.0	40	25.2	7.1	32.3	25	87
14	–50	3.0	120	8.4	2.4	10.8	75	91
15	–50	5.0	200	5.0	1.4	6.5	125	90
16	–50	7.0	280	3.6	1.0	4.6	175	88

[a] Calculated from the volume of the anodic flow channel and the flow rate.

[b] (Generation time) = (Electrolysis time) + (Residence time in **R1**)

Comparison of Divided Flow Electrochemical Reactor and Batch Electrochemical Reactor.



An electrochemical flow reactor system consisting of a divided electrochemical flow

reactor, a T-shaped micromixer (**M1**), two microtube reactors (**R1** and **R2**), and three pre-cooling units (**P1** (L = 200 cm), **P2** (200 cm) and **P3** (100 cm)) was used. The electrochemical reactor was cooled at T °C by a Peltier cooling system, and the flow microreactor system composed with **P1**, **P2**, **P3**, **R1**, **R2** and **M1** was cooled in acetone baths at T °C. During the operation, the amount of solution was monitored by sampling the solution and adjusted by changing diameter and length of tube reactor connected to the cathodic chamber. A solution of TfOH (0.05 M in Bu_4NX/CH_2Cl_2, flow rate: F mL/min) was introduced to the cathodic chamber through **P1**. A solution of substrate (0.02 M in Bu_4NX/CH_2Cl_2, flow rate: F mL/min) was introduced to the anodic chamber through **P2**. The constant current electrolysis was carried out at T °C. Current value was set to consume 1.25 F/mol of electricity. The resulting solution from anodic chamber was passed through **R1** (15 cm, residence time t^{R1} s) and introduced to **M1** (ϕ = 500 μm), where a solution of nucleophile (0.2 M in CH_2Cl_2) was also introduced (flow rate: 1/2F mL/min). The mixed solution was passed through **R2** (L_2 cm). After a steady state was reached, the product solution was collected and stirred at room temperature for 30 min. After addition of Et_3N (1 mL) to the crude, the solvent was removed under reduced pressure. Then, the solution was passed through silica plug using diethyl ether as an eluent. After concentration under reduced pressure, the crude mixture was analyzed by GC or ^1H NMR or purified by flash chromatography.

Typical Procedure for Generation and Reaction of Carbocations Using Batch Electrochemical Reactor.

The anodic oxidation was carried out using an H-type divided cell (4G glass filter) equipped with a carbon felt anode (Nippon Carbon GF-20-P7, ca 300 mg, dried at 300 °C/1 mm Hg for 3 hours before use) and a platinum plate cathode (Nilaco, ca. 10 mm × 15 mm). A Kikusui PMC350-0.2A was used as a direct current power supply for the electrolysis. In the anodic chamber were placed substrate (0.10 mmol) and supporting electrolyte solution (5 mL). In the cathodic chamber were placed TfOH (22 μL, 0.25 mmol) and supporting electrolyte solution (5 mL). The constant current electrolysis (8.0 mA) was carried out at T °C with magnetic stirring until 1.25 F of electricity was consumed (25 min). After the electrolysis, nucleophile (0.50 mmol) was added to the anodic chamber at T °C, and the resulting mixture was stirred at room temperature for 30 min. After addition of Et_3N (1 mL) to both chambers, the solution was stirred at same temperature for 10 minutes. The solution in the anodic chamber was collected and the solvent was removed under reduced pressure. Then, the residue was filtered through a short column of silica gel using Et_2O as an eluent. After removal of the solvent under reduced pressure, the crude products were analyzed by

GC or ^{1}H NMR or purified by flash chromatography.

1-Phenyl-2-(tetrahydro-2-furanyl)ethenone 3.
Electrochemical oxidation (1.25 F/mol) of **1** and subsequent reaction with **2** gave the title compound **3**. The crude was analyzed by GC using pentadecane as an internal standard. GC retention time = 20.9 min; initial oven temperature, 50 °C for 5 min; rate of temperature increase, 10 °C/min.
<Flow> Supporting electrolyte = Bu_4NBF_4; 93% yield (0.07 mmol scale, T = –50 ℃, flow rate = 7.0 mL/min, L_2 = 175 cm) and 82% yield (0.07 mmol scale, T = 0 ℃, flow rate = 7.0 mL/min, L_2 = 175 cm). Supporting electrolyte = Bu_4NOTf; 25% yield (0.06 mmol scale, T = –50 ℃, flow rate = 3.0 mL/min, L_2 = 50 cm) and 87% yield (0.06 mmol scale, T = –75 ℃, flow rate = 3.0 mL/min, L_2 = 50 cm).
<Batch> Supporting electrolyte = Bu_4NBF_4; 56% yield (T = –50 ℃) and 2% yield (T = 0 ℃). Supporting electrolyte = Bu_4NOTf; 2% yield (T = –50 ℃) and 17% yield (T = –75 ℃).

1-Phenyl-2-(tetrahydro-2*H*-pyran-2-yl)ethenone 4.
Electrochemical oxidation (1.25 F/mol) of 2-(4-fluorophenylthio)tetrahydropyran (0.21 mmol) and subsequent reaction with **2** (1.05 mmol) gave the title compound. The crude was purified by flash chromatography or analyzed by ^{1}H NMR using 1,1,2,2-tetrachloroethane as an internal standard. ^{1}H NMR (400 MHz, $CDCl_3$) δ1.37 (m, 1H), 1.55 (m, 1H), 1.74 (d, J = 12.8 Hz, 1H), 1.84 (m, 1H), 2.92 (dd, J_1 = 6.0 Hz, J_2 = 16.0 Hz, 1H), 3.28 (dd, J_1 = 6.4 Hz, J_2 = 16.0 Hz, 1H), 3.48 (t, J = 11.2 Hz, 1H), 3.94 (q, J = 8.8 Hz, 2H), 7.45 (t, J = 7.6 Hz, 2H), 7.55 (t, J = 7.6 Hz, 1H), 7.97 (d, J = 7.6 Hz, 2H). The NMR spectrum is in good agreement with that in the literature.[29]
<Flow> Supporting electrolyte = Bu_4NBF_4; 59% isolated yield (25.2 mg, T = –50 ℃, flow rate = 7.0 mL/min, L_2 = 175 cm).
<Batch> Supporting electrolyte = Bu_4NBF_4; 4% NMR yield (T = –50 ℃).

3-Methoxy-1-phenyl-1-undecanone 5.
Electrochemical oxidation (1.25 F/mol) of 1-methoxy-1-(4-fluorophenylthio)nonane and subsequent reaction with **2** gave the title compound. The crude was analyzed by GC using pentadecane as an internal standard. GC retention time = 23.9 min; initial oven temperature, 50 ℃ for 5 min; rate of temperature increase, 10 ℃/min. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.88 (t, J = 6.8 Hz, 3H), 1.20-1.44 (m, 12H), 1.50-1.63 (m, 2H), 2.93 (dd, J_1 = 5.2 Hz, J_2 = 16.0 Hz, 1H), 3.28 (dd, J_1 = 7.2 Hz, J_2 = 16.0 Hz, 1H), 3.34 (s, 3H), 3.83-3.92 (m, 1H), 7.47 (t, J = 7.6 Hz, 2H), 7.57 (t, J = 7.2 Hz, 1H), 7.97 (d, J = 6.8 Hz, 2H). The NMR

spectrum is in good agreement with that in the literature.[30]
<Flow> Supporting electrolyte = Bu_4NBF_4; 69% yield (0.07 mmol scale, T = 0 ℃, flow rate = 7.0 mL/min, L_2 = 175 cm).
<Batch> Supporting electrolyte = Bu_4NBF_4; 4% yield (T = 0 ℃).

1,1-Dimethylethyl 2-(2-oxo-2-phenylethyl)-1-pyrrolidinecarboxylate 6.
Electrochemical oxidation (1.25 F/mol) of *t*ert-butyl 2-((4-fluorophenyl)thio)pyrrolidine-1-carboxylate and subsequent reaction with **2** gave the title compound. The crude was analyzed by GC using pentadecane as an internal standard. GC retention time = 24.9 min; initial oven temperature, 50 ℃ for 5 min; rate of temperature increase, 10 ℃/min; pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.47 (s, 9H), 1.70-1.81 (m, 1H), 1.86 (m, 2H), 2.05 (m, 1H), 2.84 (m, 1H), 3.34 (s) and 3.42 (s) (total 2H, two rotamers), 3.48-3.82 (m, 1H), 4.29-4.37 (m, 1H), 7.44-7.50 (m, 2H), 7.52-7.61 (m, 1H), 8.01 (dd, J_1 = 7.2 Hz, J_2 = 11.2 Hz, 2 H). The NMR spectrum was in a good agreement with the reported one.[31]
<Flow> Supporting electrolyte = Bu_4NBF_4; 89% yield (0.07 mmol scale. T_1 and T_2 = 0 ℃, flow rate F = 7.0 mL/min, L_2 = 175 cm, T_3 = rt).
<Batch> Supporting electrolyte = Bu_4NBF_4; trace (< 1%) (T = 0 ℃).

Nucleophilic Trapping Reaction of Short-lived Carbocations.
An electrochemical flow reactor system consisting of a divided electrochemical flow reactor, a T-shaped micromixer (**M1**), two microtube reactors (**R1** and **R2**), and three pre-cooling units (**P1** (L = 200 cm), **P2** (200 cm) and **P3** (100 cm)) was used. The electrochemical reactor was cooled at T_1 ℃ by a Peltier cooling system and the precooling units **P1** and **P2** were cooled in an acetone bath at T_1 ℃. The flow microreactor system composed with **P3**, **R1**, **R2** and **M1** was cooled in an acetone bath at T_2 ℃. During the operation, the amount of solution was monitored by sampling the solution and adjusted by changing diameter and length of tube reactor connected to the cathodic chamber. A solution of TfOH (0.05 M in Bu_4NX/CH_2Cl_2, flow rate: F mL/min) was introduced to the cathodic chamber through **P1**. A solution of substrate (0.02 M in Bu_4NX/CH_2Cl_2, flow rate: F mL/min) was introduced to the anodic chamber through **P2**. The constant current electrolysis was carried out at T_1 ℃. Current value was set to consume 1.25 F/mol of electricity. The resulting solution from anodic chamber was passed through **R1** (15 cm, residence time t^{R1} s) and introduced to **M1** (ϕ = 500 μm), where a solution of nucleophile (0.2 M in CH_2Cl_2) was also introduced (flow rate: 1/2F mL/min). The mixed solution was passed through **R2** (L_2 cm). After a steady state was reached, the product solution was collected and stirred at T_3 ℃ for 30 min. After addition of triethylamine (2 mL) to the

crude, the solvent was removed under reduced pressure. Then, the solution was passed through silica plug using diethyl ether as an eluent. After concentration under reduced pressure, the crude was purified by flash chromatography.

3-Methoxy-1-phenyl-1-propanone 7.
Electrochemical oxidation (1.25 F/mol) of 1-fluoro-4-((methoxymethyl)thio)benzene (0.18 mmol) and subsequent reaction with **2** (0.90 mmol) gave the title compound. Supporting electrolyte = Bu_4NOTf, T_1 and T_2 = –50 °C, flow rate F = 3.0 mL/min, L_2 = 75 cm, T_3 = rt. The crude was purified by flash chromatography (hexane/ethyl acetate = 10/1); 23.6 mg, 80% yield, pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.25 (t, J = 6.4 Hz, 2H), 3.39 (s, 3H), 3.83 (t, J = 6.4 Hz, 2H), 7.47 (t, *J* = 7.6 Hz, 2H), 7.57 (t, *J* = 7.6 Hz, 1H), 7.97 (d, *J* = 6.8 Hz, 2H). The NMR spectrum was in a good agreement with the reported one.[34]

Methyl but-3-en-1-yl(butyl)carbamate 8.
Electrochemical oxidation (1.25 F/mol) of butyl(((4-fluorophenyl)thio)methyl)carbamate (0.07 mmol) and subsequent reaction with allyltrimethylsilane (0.35 mmol) gave the title compound. Supporting electrolyte = Bu_4NBF_4, T_1 and T_2 = 0 °C, flow rate F = 7.0 mL/min, L_2 = 175 cm, T_3 = rt. The crude was analyzed by GC using hexadecane as an internal standard and indicated quantitative yield. GC retention time = 20.1 min; initial oven temperature, 50 °C for 5 min; rate of temperature increase, 10 °C /min; pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, *J* = 6.8 Hz, 3 H), 1.22-1.38 (m, 2H), 1.42-1.56 (m, 2H), 2.21-2.35 (m, 2H), 3.11-3.35 (m, 4H), 3.68 (s, 3H), 5.00-5.12 (m, 2H), 5.68-5.85 (m, 1H). The NMR spectrum was in a good agreement with the reported one.[35]

Methyl 3-(1,3-dioxoisoindolin-2-yl)-2,2-dimethylpropanoate 9.
Electrochemical oxidation (1.25 F/mol) of 2-(((4-fluorophenyl)thio)methyl)isoindoline -1,3-dione (0.18 mmol) and subsequent reaction with dimethylketene methyl trimethylsilyl acetal (0.90 mmol) gave the title compound. Supporting electrolyte = Bu_4NOTf; T_1 and T_2 = –50 °C, flow rate F = 3.0 mL/min, L_2 = 75 cm, T_3 = rt. The aliquot was purified by flash chromatography (hexane/ethyl acetate = 5/1); 41.4 mg, 88% yield, colorless solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.25 (s, 6H), 3.73 (s, 3H), 3.85 (s, 2H), 7.72-7.74 (m, 2H), 7.84-7.86 (m, 2H). The NMR spectrum was in a good agreement with the reported one.[36]

2-(3-Oxo-3-phenylpropyl)isoindoline-1,3-dione 10.
Electrochemical oxidation (1.25 F/mol) of 2-(((4-fluorophenyl)thio)methyl)isoindoline -1,3-dione (0.18 mmol) and subsequent reaction with **2** (0.90 mmol) gave the title compound. Supporting electrolyte = Bu_4NOTf; T_1 and T_2 = –50 °C, flow rate F = 3.0

mL/min, L_2 = 75 cm, T_3 = rt. The aliquot was purified by flash chromatography (hexane/ethyl acetate = 5/1); 31.8 mg, 63% yield, white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.44 (t, *J* = 7.0 Hz, 2H), 4.15 (t, *J* = 7.5 Hz, 2H), 7.45 (t, *J* = 7.5 Hz, 2H), 7.56 (t, *J* = 7.0 Hz, 1H), 7.71-7.75 (m, 2H), 7.84-7.87 (m, 2H), 7.93-7.97 (m, 2H). The NMR spectrum was in a good agreement with the reported one.[37]

(4-Fluorophenyl)(1-phenylbut-3-en-1-yl)sulfane 11.

Electrochemical oxidation (1.25 F/mol) of *S*, *S'*-bis(*p*-fluorophenyl)benzaldehydedithio-acetal (0.21 mmol) and subsequent reaction with allyltrimethylsilyl (1.05 mmol) gave the title compound. Supporting electrolyte = Bu_4NBF_4; T_1 and T_2 = –50 °C, flow rate F = 7.0 mL/min, L_2 = 175 cm, T_3 = rt. The aliquot was purified by flash chromatography (ethyl acetate); 49.7 mg, 92% yield, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.68 (t, *J* = 7.5 Hz, 2H), 4.08 (t, *J* = 7.5 Hz, 1H), 4.98-5.08 (m, 2H), 5.72 (m, 1H), 6.85-6.91 (m, 2H), 7.14-7.28 (m, 7H). The NMR spectrum was in a good agreement with the reported one.[26]

Flash Generation of Glycosyl Cation Equivalents.

A flow electrochemical reactor system consisting of a divided electrochemical flow reactor, a T-shaped micromixer (**M1**), two microtube reactors (**R1** and **R2**), and three pre-cooling units (**P1** (L = 200 cm), **P2** (200 cm) and **P3** (100 cm)) was used. The electrochemical reactor was cooled at T °C by a Peltier cooling system, and the flow microreactor system composed with **P1**, **P2**, **P3**, **R1**, **R2** and **M1** was cooled in acetone baths at T °C. During the operation, the amount of solution was monitored by sampling the solution and adjusted by changing diameter and length of tube reactor connected to the cathodic chamber. A solution of TfOH (0.05 M in $Bu_4NB(C_6F_5)_4/CH_2Cl_2$, flow rate: F mL/min) was introduced to the cathodic chamber through **P1**. A solution of thioglycoside (0.02 M in $Bu_4NB(C_6F_5)_4/CH_2Cl_2$, flow rate: F mL/min) was introduced to the anodic chamber through **P2**. The constant current electrolysis was carried out at T °C. Current value was set to consume 1.25 F/mol of electricity. The resulting solution from anodic chamber was passed through **R1** (15 cm, residence time t^{R1} s) and introduced to **M1** (ϕ = 500 μm), where a solution of methanol (0.2 M in CH_2Cl_2) was also introduced (flow rate: 1/2F mL/min). The mixed solution was passed through **R2** (L_2 cm, residence time t^{R2} = 8 s). After a steady state was reached, the product solution was collected and stirred at room temperature for 30 min. After addition of Et_3N (2 mL) to the crude, the crude solution was passed through silica plug using Et_2O as an eluent. After concentration under reduced pressure, the crude mixture was analyzed by ^{1}H NMR, using 1,1,2,2-tetrachloroethane as an internal standard, or purified by flash chromatography. The results are summarized in Table S4.

Methyl tetra-*O*-methyl-α-D-glucoside 12α and methyl tetra-*O*-methyl-β-D-glucoside 12β.

Electrochemical oxidation (1.25 F/mol) of 4-fluorophenyl 2,3,4,6-tetra-*O*-methyl-1-thio-β -D-glucopyranoside (0.21 mmol) and subsequent reaction with MeOH (1.05 mmol) gave the title compound. The crude was purified by flash chromatography or analyzed by ^{1}H NMR using 1,1,2,2-tetrachloroethane as an internal standard, pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) **12α** δ 3.15-3.24 (m, 2H), 3.41 (s, 3H), 3.42 (s, 3H), 3.47-3.53 (m, 1H), 3.51 (s, 3H), 3.54 (s, 3H), 3.56-3.61 (m, 3H), 3.63 (s, 3H), 4.83 (d, J = 4.0 Hz, 1H). The NMR spectrum was in a good agreement with the reported one.[32] ^{1}H NMR (400 MHz, $CDCl_3$) **12β** δ 2.95-3.01 (m, 1H), 3.11-3.19 (m, 2H), 3.24-3.30 (m, 1H), 3.41 (s, 3H), 3.50-3.58 (m, 1H), 3.52 (s, 3H), 3.53 (s, 3H), 3.57 (s, 3H), 3.62-3.66 (m, 1H), 3.63 (s, 3H), 4.14 (d, J = 7.5 Hz, 1H).

The NMR spectrum was in a good agreement with the reported one.[33]

Table S4. Effect of Generation Time on a Glycosyl Cation Equivalent.

entry	T [°C]	F [mL/min]	current [mA]	electrolysis time [s] [a]	t^{R1} [s]	generation time [s] [b]	L_2 [cm]	yield of **12** (α/β) [%] [c]
1	–50	batch	8	1500	-	1500	-	41 (58/42)
2	–50	3.0	120	8.4	2.4	10.8	75	60 (66/34)
3	–50	5.0	200	5.0	1.4	6.5	125	65 (57/43)
4	–50	7.0	280	3.6	1.0	4.6	175	73 (60/40)
5	–75	7.0	280	3.6	1.0	4.6	175	78 (65/35)[d]

[a] Calculated from the volume of the anodic flow channel and the flow rate.

[b] (Generation time) = (Electrolysis time) + (Residence time in R1)

[c] Determined by ^{1}H NMR yield. [d] Yield of the Isolated compound.

Methyl-6-*O*-(2,3,4,6-tetra-*O*-methyl-α-D-glucopyranosyl)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside 13α and Methyl-6-*O*-(2,3,4,6-tetra-*O*-methyl-β-D-glucopyranosyl)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside 13β.

Electrochemical oxidation (1.25 F/mol) of 4-fluorophenyl 2,3,4,6-tetra-*O*-methyl-1-thio-β-D-glucopyranoside (0.14 mmol) and subsequent reaction with methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (0.70 mmol) gave the title compound. Supporting electrolyte = $Bu_4NB(C_6F_5)_4$, T_1 and T_2 = –75 °C, flow rate F = 7.0 mL/min, L_2 = 175 cm, T_3 = –78 °C. The crude was purified by flash chromatography (hexane/ethyl acetate = 2/1); 80.7 mg, 84% yield (α/β = 31/69); white solid. ^{1}H NMR (400 MHz, $CDCl_3$) **13α** δ 3.10-3.16 (m, J =

1H), 3.17-3.19 (m, 1H), 3.37 (s, 3H), 3.38 (s, 6H), 3.44-3.66 (m, 6H), 3.51 (s, 3H), 3.61 (s, 3H), 3.72-3.81 (m, 3H), 3.98-4.04 (m, 1H), 4.22 (d, J = 7.9 Hz, 1H), 4.62-4.66 (m, 2H), 4.82-4.91 (m, 3H), 4.97 (d, J = 10.6 Hz, 1H), 4.99 (d, J = 3.2 Hz, 1H), 7.24-7.37 (m, 15H). ^{1}H NMR (400 MHz, $CDCl_3$) **13β** δ 3.00-3.16 (m, 3H), 3.22-3.27 (m, 1H), 3.36 (s, 3H), 3.37 (s, 3H), 3.48-3.59 (m, 4H), 3.51 (s, 3H), 3.57 (s, 3H), 3.61 (s, 3H), 3.66-3.72 (m, 1H), 3.73-3.82, (m, 1H), 3.96-4.02 (m, 1H), 4.13 (dd, J_1 = 1.8, J_2 = 10.6 Hz, 1H), 4.20 (d, J = 3.6 Hz, 1H), 4.56 (d, J = 3.5 Hz, 1H), 4.63-4.67 (m, 2H), 4.77-4.88 (m, 3H), 4.99 (d, J = 11.0 Hz, 1H), 7.26-7.38 (m, 15H). The NMR spectrum were in a good agreement with the reported one.[8(a)]

1-(2,3,4,6-Tetra-*O*-methyl-β-D-glucopyranosyl)naphthalen-2-ol 14.

Electrochemical oxidation (1.25 F/mol) of 4-fluorophenyl 2,3,4,6-tetra-*O*-methyl-1-thio-β -D-glucopyranoside (0.14 mmol) and subsequent reaction with 2-naphthol (0.70 mmol) gave the title compound. Supporting electrolyte = $Bu_4NB(C_6F_5)_4$, T_1 = –75 °C, T_2 = 0 °C, flow rate F = 7.0 mL/min, L_2 = 175 cm, T_3 = 0 °C. The aliquot was purified by flash chromatography (hexane/ethyl acetate = 5/1); 40.3 mg, 79% yield, pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.71 (s, 3H), 3.35-3.55 (m, 4H), 3.42 (s, 3H), 3.60-3.67 (m, 2H), 3.62 (s, 3H), 3.68 (s, 3H), 5.25 (d, J = 9.7 Hz, 1H), 7.14 (d, J = 9.2 Hz, 1H), 7.30 (t, J = 7.0 Hz, 1H), 7.44 (t, J = 7.0 Hz, 1H), 7.71-7.76 (m, 2H), 7.97 (d, J = 8.4 Hz, 1H), 8.52 (s, 1H). The NMR spectrum was in a good agreement with the reported one.[38]

Methyl 2,3,5-tri-O-methyl-β-D-ribofuranoside 15.

Electrochemical oxidation (1.25 F/mol) of 4-fluorophenyl 2,3,5-tri-*O*-methyl-β-D-thioribo-furanoside (0.21 mmol) and subsequent reaction with MeOH (1.05 mmol) gave the title compound. Supporting electrolyte = $Bu_4NB(C_6F_5)_4$, T_1 and T_2 = –75 °C, flow rate F = 7.0 mL/min, L_2 = 175 cm, T_3 = rt. The crude was purified by flash chromatography (hexane/ethyl acetate = 5/1 to 1/1); 25.9 mg, 60% yield (β only), pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.39 (s, 3H), 3.41 (s, 3H), 3.42 (s, 3H), 3.44-3.49 (m, 1H, 3.50 (s, 3H), 3.53-3.58 (m, 1H), 3.72 (d, J = 4.8 Hz, 1H), 3.79-3.83 (m, 1H), 4.15-4.20 (m, 1H), 4.92 (s, 3H). The NMR spectrum was in a good agreement with the reported one.[39]

Methyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-β-D-glucopyranosyl-(1 → 6)-2,3,4-tri-*O*-benzyl-α-D-glucopyranoside 16.

Electrochemical oxidation (1.25 F/mol) of 4-fluorophenyl 3,4,6-tri-*O*-acetyl-2-deoxy-2-phthalimido-1-thio-β-D-glucopyranoside (0.14 mmol) and subsequent reaction with methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside (0.70 mmol) gave the title compound. Supporting electrolyte = $Bu_4NB(C_6F_5)_4$, T_1 and T_2 = –75 °C, flow rate = 7.0 mL/min, L_2 = 175 cm, T_3

= –50 °C. The aliquot was purified by flash chromatography (hexane/ethyl acetate = 1/1) and GPC; 70.5 mg, 57% yield, white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.85 (s, 3H), 2.03 (s, 3H), 2.08 (s, 3H), 3.17 (s, 3H), 3.24 (pseudo t, J = 9.2 Hz, 1H), 3.39 (dd, J_1 = 3.6Hz, J_2 = 9.6 Hz, 1H), 3.66 (d, J = 8.8 Hz, 1H), 3.84-3.90 (m, 2H), 4.07-4.13 (m, 2H), 4.17 (dd, J_1 = 2.6 Hz, J_2 = 12.3 Hz, 1H), 4.33 (dd, J_1 = 4.8 Hz, J_2 = 11.9 Hz, 1H), 4.36-4.42 (m, 3H), 4.57 (d, J = 12.3 Hz, 1H), 4.65 (d, J = 10.6 Hz, 1H), 4.72 (d, J = 11.9 Hz, 1H), 4.86 (d, J = 10.6 Hz, 1H), 5.18 (pseudo t, J = 9.2 Hz, 1H), 5.44 (d, J = 8.4 Hz, 1H), 5.79 (dd, J_1 = 9.2 Hz, J_2 = 10.6 Hz, 1 H), 7.00-7.05 (m, 2H), 7.20-7.35 (m, 15H), 7.55 (br s, 2H). The NMR spectrum was in a good agreement with the reported one.[40]

Flash Generation of the Ferrier Intermediate in Flow Electrochemical Reactor System.

A flow electrochemical flow reactor system consisting of a divided electrochemical flow reactor, a T-shaped micromixer (**M1**), two microtube reactors (**R1** and **R2**), and three pre-cooling units (**P1** (L = 200 cm), **P2** (200 cm) and **P3** (100 cm)) was used. The electrochemical reactor was cooled at –75 °C by a Peltier cooling system, and the flow microreactor system composed with **P1**, **P2**, **P3**, **R1**, **R2** and **M1** was cooled in acetone baths at –75 °C. During the operation, the amount of solution was monitored by sampling the solution and adjusted by changing diameter and length of tube reactor connected to the cathodic chamber. A solution of TfOH (0.05 M in Bu_4NBF_4/CH_2Cl_2, flow rate: F mL/min) was introduced to the cathodic chamber through **P1**. A solution of tri-*O*-methyl-D-glucal (0.02 M in Bu_4NBF_4/CH_2Cl_2, flow rate: F mL/min) was introduced to the anodic chamber through **P2**. The constant current electrolysis was carried out at –75 °C. Current value was set to consume 1.25 F/mol of electricity. The resulting solution from anodic chamber was passed through **R1** (L_1 cm, residence time t^{R1} s) and introduced to **M1** (ϕ = 500 μm), where a solution of allyltrimethylsilane (0.2 M in CH_2Cl_2) was also introduced (flow rate: 1/2F mL/min). The mixed solution was passed through **R2** (L_2 cm, residence time t^{R2} = 8 s). After a steady state was reached, the product solution was collected and stirred at room temperature for 30 min. After addition of Et_3N (1 mL) to the crude, the solvent was removed under reduced pressure. To the crude product, Et_2O and tridecane were added, and the mixture was analyzed by GC. The results are summarized in Table S5.

Table S5. Effect of Electrolysis Time and Generation Time on Generation of the Ferrier Intermediates.

entry	flow rate F [mL/min]	current [mA]	electrolysis time [s] [a]	L_1 [cm]	t^{R1} [s]	generation time [s] [b]	L_2 [cm]	yield of **17** (α/β) [%]
1	batch	8	1500	-	-	1500	-	11 (91/9)
2	1.0	40	25	15	7	32	25	32 (94/6)
3	3.0	120	8	150	24	32	75	41 (93/7)
4	5.0	200	5	290	27	32	125	56 (93/7)
5	7.0	280	4	425	28	32	175	60 (92/8)
6	7.0	280	4	115	7	11	175	66 (92/8)
7	7.0	280	4	15	1	5	175	71 (95/5)[c]

[a] Calculated from the volume of the anodic flow channel and the flow rate.

[b] (Generation time) = (Electrolysis time) + (Residence time in **R1**)

[c] Yield of the Isolated compound.

(2*R*,3*S*,6*R*)-3,6-Dihydro-3-methoxy-2-(methoxymethyl)-6-(2-propen-1-yl)-2*H*-pyran 17α and (2*R*,3*S*,6*S*)-3,6-Dihydro-3-methoxy-2-(methoxymethyl)-6-(2-propen-1-yl)-2*H*-pyran 17β.

Electrochemical oxidation (1.25 F/mol) of tri-*O*-methyl-D-glucal (0.07 mmol) and subsequent reaction with allyltrimethylsilane gave the title compound. The crude was analyzed by GC using tridecane as an internal standard. GC retention time = 14.9 min (β-isomer) and 15.8 min (α-isomer); initial oven temperature, 50 °C for 5 min; rate of temperature increase, 10 °C/min. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.26-2.35 (m, 1H), 2.43-2.52 (m, 1H), 3.40 (s, 3H), 3.41 (s, 3H), 3.54-3.62 (m, 2H), 3.69-3.75 (m, 2H), 4.20-4.27 (m, 1H), 5.05-5.14 (m, 2H), 5.78-5.96 (m, 3H). The NMR spectrum was in a good agreement with the reported one.[41]

Substrate Scope on the Ferrier Intermediates.

A flow electrochemical reactor system consisting of a divided electrochemical flow reactor, a T-shaped micromixer (**M1**), two microtube reactors (**R1** and **R2**), and three pre-cooling units (**P1** (L = 200 cm), **P2** (200 cm) and **P3** (100 cm)) was used. The reactor was cooled at −75 °C by a Peltier cooling system, and the flow microreactor system composed with **P1**, **P2**, **P3**, **R1**, **R2** and **M1** was cooled in acetone baths at −75 °C. During the operation, the amount of solution was monitored by sampling the solution and adjusted by changing diameter and length of tube reactor connected to the cathodic chamber. A solution of TfOH (0.05 M in Bu_4NBF_4/CH_2Cl_2, flow rate: 7.0 mL/min) was introduced to the cathodic

chamber through **P1**. A solution of substrate (0.02 M in Bu_4NBF_4/CH_2Cl_2, flow rate: 7.0 mL/min) was introduced to the anodic chamber through **P2**. The constant current electrolysis was carried out at −75 °C. Current value was set to consume 1.25 F/mol of electricity. The resulting solution from anodic chamber was passed through **R1** (L_1 = 15 cm, residence time t^{R1} = 1.0 s) and introduced to **M1** (ϕ = 500 μm), where a solution of nucleophile (0.2 M in CH_2Cl_2) was also introduced (flow rate: 3.5 mL/min). The mixed solution was passed through **R2** (L_2 = 175 cm, residence time t^{R2} = 8 s). After a steady state was reached, the product solution was collected and stirred at room temperature for 30 min. After addition of Et_3N (2 mL) to the crude, the solvent was removed under reduced pressure. Then, the solution was passed through silica plug using Et_2O as an eluent. After concentration under reduced pressure, the crude was purified by flash chromatography.

((2*R*,3*S*,6*R*)-3-Acetoxy-6-allyl-3,6-dihydro-2*H*-pyran-2-yl)methyl acetate 18α and ((2*R*,3*S*,6*S*)-3-acetoxy-6-allyl-3,6-dihydro-2*H*-pyran-2-yl)methyl acetate 18β.
Electrochemical oxidation (1.25 F/mol) of tri-*O*-acetyl-D-glucal (0.21 mmol) and subsequent reaction with allyltrimethylsilane (1.05 mmol) gave the title compound. The crude was purified by flash chromatography (hexane/ethyl acetate = 5/1); 39.5 mg, 74% (α/β = 94/6) isolated yield, pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.08 (s, 6H), 2.27-2.50 (m, 2H), 3.91-3.97 (m, 1H), 4.11-4.30 (m, 3H), 5.08-5.16 (m, 3H), 5.75-5.95 (m, 3H)**.** The NMR spectrum was in a good agreement with the reported one.[42]

((2*R*,3*S*,6*S*)-3-Acetoxy-6-(((2*R*,3*R*,4*S*,5*R*,6*S*)-3,4,5-tris(benzyloxy)-6-methoxytetrahydro-2*H*-pyran-2-yl)methoxy)-3,6-dihydro-2*H*-pyran-2-yl)methyl acetate 19α and ((2*R*,3*S*,6*R*)-3-acetoxy-6-(((2*R*,3*R*,4*S*,5*R*,6*S*)-3,4,5-tris(benzyloxy)-6-methoxytetrahydro-2*H*-pyran-2-yl)methoxy)-3,6-dihydro-2*H*-pyran-2-yl)methyl acetate 19β.
Electrochemical oxidation (1.25 F/mol) of tri-*O*-acetyl-D-glucal (0.14 mmol) and subsequent reaction with methyl 2,3,4-tri-O-benzyl-α-D-glucopyranoside (0.70 mmol) gave the title compound. The crude was purified by flash chromatography (hexane/ethyl acetate = 2/1) and GPC; 72.0 mg, 76% (α/β = 81/19) isolated yield, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.00 (s, 3H), 2.07 (s, 3H), 3.38 (s, 3H), 3.51-3.62 (m, 2H), 3.69-3.80 (m, 2H), 3.96-4.06 (m, 4H), 4.14-4.24 (m, 1H), 4.60-4.70 (m, 3H), 4.76-4.84 (m, 2H), 4.96 (dd, J_1 = 11.0 Hz, J_2 = 22.0 Hz, 2H), 5.06-5.08 (m) and 5.11 (s) (total 1H), 5.17 (m) and 5.30 (d, 9.7 Hz) (total = 1H), 5.85 (s, 1H), 7.26-7.40 (m, 15H). The NMR spectrum was in a good agreement with the reported one.[43]

Methyl (*R*)-4-((2*R*,5*S*,6*R*)-5-acetoxy-6-(acetoxymethyl)-5,6-dihydro-2*H*-pyran-2-yl)-2 (((benzyloxy)carbonyl)amino)butanoate 20.

Electrochemical oxidation (1.25 F/mol) of tri-*O*-acetyl-D-glucal (0.14 mmol) and subsequent reaction with *N*-benzyloxycarbonyl-L-serine methyl ester (0.70 mmol) gave the title compound. The crude was purified by flash chromatography (hexane/ethyl acetate = 2/1 to 1/1); 40.8 mg, 63% (α only) isolated yield, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.06 (s, 3H), 2.08 (s, 3H), 3.77 (s, 3H), 3.97-4.08 (m, 3H), 4.18-4.22 (m, 2H), 4.51-4.60 (m, 1H), 4.98 (br s, 1H), 5.14 (s, 2H), 5.27 (d, J = 9.7Hz, 1H), 5.72-5.77 (m, 1H), 5.83-5.91 (m, 1H), 7.30-7.40 (m, 5H). The NMR spectrum was in a good agreement with the reported one.[44]

((2*R*,3*S*)-3-Acetoxy-6-azido-3,6-dihydro-2*H*-pyran-2-yl)methyl acetate 21 and ((2*R*,3*S*)-3-acetoxy-4-azido-3,4-dihydro-2*H*-pyran-2-yl)methyl acetate 21'.

Electrochemical oxidation (1.25 F/mol) of tri-*O*-acetyl-D-glucal (0.21 mmol) and subsequent reaction with trimethylsilyl azide (1.05 mmol) gave the title compound. The additional stirring after flow was performed at −30 °C for 10 min. The crude was purified by flash chromatography (hexane/ethyl acetate = 5/1); 27.8 mg, 33% (**21α**/**21β** = 98/2) and 19% (**21'α**/**21'β** = 42/58) isolated yield, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.09-2.15 (s, 4-isomer), 4.00-4.02 (m, C-1, β), 4.05-4.41 (m, C-1 and C-3), 4.81 (dd, J_1 = 6.2 Hz, J_2 = 2.6 Hz, C-3, β), 4.90 (t, J = 5.7 Hz, C-3, α), 4.99-5.04 (m, C-1, β), 5.10 (dd, J_1 = 10.6 Hz, J_2 = 4.4 Hz, C-3, α), 5.17 (dd, J_1 = 9.0 Hz, J_2 = 7.5 Hz, C-3, β), 5.24-5.28 (m, C-1, β), 5.30-5.35 (m, C-1, α), 5.58 (br s, C-1, α), 5.76-5.81 (m, C-1, α), 5.84-5.90 (m, C-1, β), 5.93-5.98 (m, C-1, α), 6.01-6.07 (m, C-1, b), 6.50 (dd, J_1 = 6.2 Hz, J_2 = 1.8 Hz, C-3, β), 6.53 (d, J = 6.2 Hz, C-3, α). The NMR spectrum was in a good agreement with the reported one.[45]

((2*R*,3*R*,6*R*)-3-Acetoxy-6-allyl-3,6-dihydro-2*H*-pyran-2-yl)methyl acetate 22.

Electrochemical oxidation (1.25 F/mol) of tri-*O*-acetyl-D-galactal (0.21 mmol) and subsequent reaction with allyltrimethylsilane (1.05 mmol) gave the title compound. The crude was purified by flash chromatography (hexane/ethyl acetate = 5/1); 34.2 mg, 64% (α only) isolated yield, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.07 (s, 3H), 2.08 (s, 3H), 2.23-2.50 (m, 2H), 4.12-4.17 (m, 1H), 4.19-4.25 (m, 2H), 4.33-4.39 (m, 1H), 5.08 (dd, J_1 = 2.6 Hz, J_2 = 4.8 Hz, 1H), 5.10-5.17 (m, 2H), 5.80-5.91 (m, 1H), 5.96-6.08 (m,2H). The NMR spectrum was in a good agreement with the reported one.[46]

(2*S*,3*R*,6*S*)-6-(Benzyloxy)-2-(2-oxopropoxy)-3,6-dihydro-2*H*-pyran-3-yl acetate 23.

Electrochemical oxidation (1.25 F/mol) of tri-*O*-acetyl-D-galactal (0.14 mmol) and

subsequent reaction with benzyl alcohol (0.70 mmol) gave the title compound. The crude was purified by flash chromatography (hexane/ethyl acetate = 5/1 to 1/1) and GPC; 54% (α only) isolated yield, pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.07 (s, 3H), 2.08 (s, 3H), 4.18-4.28 (m, 2H), 4.40-4.45 (m, 1H), 4.59 (d, J = 11.4 Hz, 1H), 4.82 (d, J = 11.4 Hz, 1H), 5.04 (dd, J_1 = 2.6 Hz, J_2 = 5.5 Hz, 1H), 5.17 (d, J = 3.1 Hz, 1H), 6.05 (dd, J_1 = 3.1 Hz, J_2 = 10.1 Hz, 1H), 6.13 (dd, J_1 = 5.3 Hz, J_2 = 10.1 Hz, 1H), 7.28-7.34 (m, 1H), 7.36 (d, J = 4.4 Hz, 4H). The NMR spectrum was in a good agreement with the reported one.[47]

Continuous Production of *N*-Boc Methylphenidate.

A flow electrochemical flow reactor system consisting of a divided electrochemical flow reactor, a T-shaped micromixer (**M1**), two microtube reactors (**R1** and **R2**), and three pre-cooling units (**P1** (L = 200 cm), **P2** (200 cm) and **P3** (100 cm)) was used. The electrochemical reactor was cooled at −50 °C by a Peltier cooling system and two pre-cooling units were cooled in acetone baths at −50 °C. The flow microreactor system composed with **P3**, **R1**, **R2** and **M1** was cooled in acetone bath at 0 °C. The syringe pumps were replaced with plunger pumps (Shimadzu, LC-20AD) that were suitable for long time operation. During the operation, the amount of solution was monitored by sampling the solution and adjusted by changing diameter and length of tube reactor connected to the cathodic chamber. A solution of TfOH (0.05 M in Bu_4NBF_4/CH_2Cl_2, flow rate: 7.0 mL/min) was introduced to the cathodic chamber through **P1**. A solution of *tert*-butyl 2-(*p*-fluorothio)piperidine-1-carboxylate (0.02 M in Bu_4NBF_4/CH_2Cl_2, flow rate: 7.0 mL/min) was introduced to the anodic chamber through **P2**. The constant current electrolysis was carried out at −50 °C. Current value was set to consume 1.25 F/mol of electricity. The resulting solution from anodic chamber was passed through **R1** (15 cm, residence time t^{R1} = 1.0 s) and introduced to **M1** (ϕ = 500 μm), where a solution of phenyl ketene methyl(trimethylsilyl)acetal (0.2 M in CH_2Cl_2) was also introduced (flow rate: 3.5 mL/min). The mixed solution was passed through **R2** (300 cm, residence time t^{R2} = 13.5 s). After a steady state was reached, aliquots of the crude reaction solution were collected to a vessel containing Et_3N (20 mL) for 10 minutes. Continuous operation was carried out for 60 min, and the vessels were changed every 10 min. The solvent was removed under reduced pressure, then the Et_2O (100 mL) was added, and the crude solution was filtered. After concentration under reduced pressure, 1,1,2,2-tetrachloroethane was added to the residue and ^{1}H NMR analysis was performed. Then, the residue was purified by flash chromatography (hexane/ethyl acetate = 10/1) to obtain *N*-Boc-methylphenidate (2.34g, 7.0 mmol, 83% yield).

***N*-Boc-methylphenidate 24.**

Electrochemical oxidation (1.25 F/mol) of *tert*-butyl 2-(*p*-fluorothio)piperidine-1-carboxylate (8.4 mmol) and subsequent reaction with phenyl ketene methyl(trimethylsilyl)acetal (42.0 mmol) gave the title compound. The crude was purified by flash chromatography (hexane/ethyl acetate = 10/1); 83% yield, pale yellow oil. The compound was characterized as a mixture of two diastereomers (*threo*/*erythro* = 3/1 determined by ^{1}H NMR) and gave complicated NMR signals, because of the presence of rotamers around the tertiary amide. TLC: Rf = 0.30 (hexane/ethyl acetate = 10/1) ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.15-1.30 (br s, 3H), 1.30-1.44 (br, 2H), 1.48-1.57 (br, 9H), 1.57-1.87 (br, 3H), 2.71 (m) and 3.01 (m) (total 1H), 3.62 (s) and 3.67 (s) (total 3H), 3.93-4.23 (m, 2H), 4.80-5.22 (brd, 1H), 7.20-7.50 (m, 5H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.7, 19.1, 24.9-25.5 (m), 28.0, 28.2, 38.3, 39.8, 50.5, 50.8, 51.4, 51.8, 52.0, 52.8, 53.2, 54.2, 77.2, 79.1-79.5 (m), 127.6, 128.2, 128.6, 128.9, 135.6, 136.1, 136.2, 154.1, 154.4, 172.2, 172.9. HRMS (ESI) calcd for $C_{19}H_{27}NO_4Na$ [M+Na^+]: 356.1832, found 356.1825; IR ($CHCl_3$ solution) ν_{max}: 1682, 1737 cm^{-1}.

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Chapter 2

Rapid Access to Cationic Organic Triflates Based on Flash Electrolysis in Flow

Abstract

Flash electrochemical generation of highly unstable arylbis(arylthio)sulfonium triflates $[ArS(ArSSAr)]^+$ $[OTf]^-$ was achieved within 10 seconds using a divided-type flow electrochemical reactor, enabling one-flow access to various cationic organic triflates. $[ArS(ArSSAr)]^+$ $[OTf]^-$ served as thiotriflating reagents for alkynes and mediator for sequential generation of short-lived cyclic oxocarbenium triflates in an integrated flow reactor system, applying to stability study of the intermediate and to rapid glycosylation.

Introduction

Organic trifluoromethanesulfonate (triflate, $[OTf]^-$) species are widely utilized in organic chemistry.[1] In general, they are highly reactive cationic intermediates or equivalents due to the outstanding nucleofugal property of triflate, and play a key role in the construction of diverse molecular skeletons.[2] Traditionally, they are generated in the presence of nucleophiles by the treatment of precursors with chemical activators such as metal triflates,[3] triflic acid (TfOH)[4] or triflic anhydride (Tf_2O)[5], and immediately reacted to avoid the decomposition.

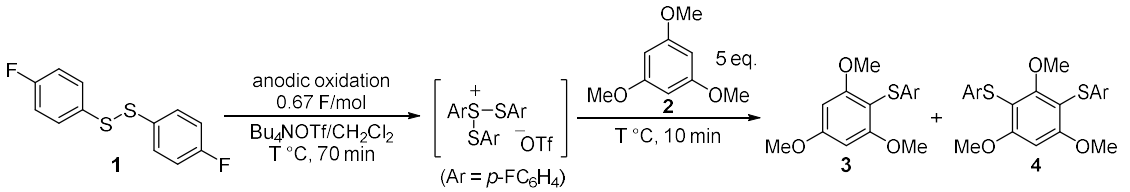
Electrochemical oxidation is a powerful and straightforward method for utilizing reactive cationic intermediates.[6] This technique, involving forced electron transfer which is initiated at the surface of electrodes, uses electrons as a mild and traceless activator, enabling irreversible generation. Among them, the cation pool method that involves generation and accumulation of unstable organic cations in the absence of nucleophiles under cryogenic conditions have been widely studied due to its flexibility and versatility of nucleophiles.[7] However, the applicability of this method is strongly influenced by the stability of generated cations, because the long electrolysis duration caused by a small surface-to-volume ratio of the electrodes in batch reactors often resulted in the decomposition of unstable cations. In fact, detailed studies on cationic organic triflate intermediates in the cation pool method have been limited to those on glycosyl triflates,[8] presumably because such intermediates were too unstable to accumulate. Moreover, although the indirect cation pool method that allows rapid generation of organic cations mediated by anodically generated reactive intermediates have been developed by Yoshida and co-workers, this method must use accumulable cations with counter anions of $[BF_4]^-$ or $[B(C_6F_5)_4]^-$.[9]

To overcome this challenge, the key would be the significant shortening of the reaction process, that is, the rapid completion of electrolysis and immediate transport to the place where the reaction takes place. From this point of view, the combination of electrochemistry and flow chemistry seems to be a promising solution.[10] This chapter describes the flash electrochemical generation of highly unstable arylbis(arylthio)sulfonium triflates within 10 s in the flow electrochemical reactor system. This allows rapid access to various organic triflates including vinyl triflates, oxocarbenium triflates and glycosyl triflates.

Results and Discussion

Initially, electrochemical generation and accumulation of arylbis(arylthio)sulfonium triflate $[ArS(ArSSAr)]^+$ $[OTf]^-$ was examined by using a conventional batch electrochemical reactor (Table 1). Yoshida and co-workers reported that $[ArS(ArSSAr)]^+$ $[BF_4]^-$ was accumulable in solution at −78 °C and reacted with aromatic nucleophiles to give arylthiolated products in excellent yields.[11] Diaryldisulfide ArSSAr (Ar = *p*-FC_6H_4) **1** was anodically oxidized until 0.67 F/mol of electricity was consumed in Bu_4NOTf/CH_2Cl_2 system; 0.67 F/mol is the theoretical amount of electricity required to convert ArSSAr to $[ArS(ArSSAr)]^+$. After electrolysis, 5 equivalents of 1,3,5-trimethoxybenzene **2** in CH_2Cl_2 was added and the mixture was stirred for 10 min, followed by treatment with triethylamine Et_3N to obtain arylthiolated products **3** and **4**. Trials under cryogenic conditions at −78 °C and −50 °C gave unsatisfactory yields (Table 1, entries 1 and 2). When the electrolysis was performed at 0 °C, a significant decrease in the yield was observed (Table 1, entry 3). These results suggest that $[ArS(ArSSAr)]^+$ $[OTf]^-$ is highly unstable and decomposes during prolonged electrolysis time.

Table 1. Electrochemical Generation and Accumulation of $[ArS(ArSSAr)]^+$ $[OTf]^-$ Using a Batch Electrochemical Reactor.



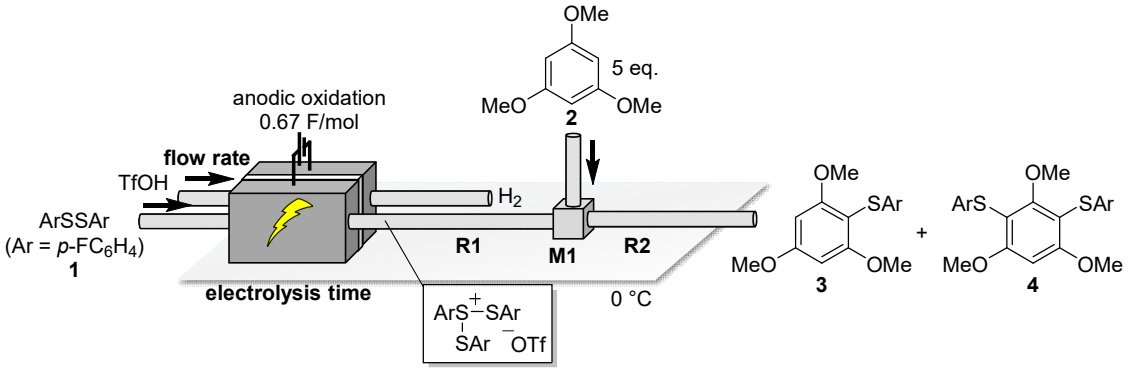
entry	temperature T [°C]	yield of **3** [%][a]	yield of **4** [%][a]
1	−78	61	0
2	−50	58	2
3	0	44	3

Conditions: **1** (0.50 mmol), current = 8 mA, **2** (2.5 mmol). [a] Determined by GC.

Subsequently, the flash generation and reaction of $[ArS(ArSSAr)]^+$ $[OTf]^-$ in a flow electrochemical reactor system was examined (Table 2). The flow electrochemical reactor system consists of a divided-type flow electrochemical reactor and microreactors. In the flow electrochemical reactor, both the anodic and cathodic stainless-steel cells were divided by a diaphragm comprised of glass filters and PTFE membranes, and the electrolysis temperature was controlled by a Peltier cooling system. For the flow system, a solution of **1** and TfOH in Bu_4NOTf/CH_2Cl_2 were introduced by syringe pumping into the anodic and

cathodic cells respectively. Constant-current electrolysis was performed at 0 °C, and $[ArS(ArSSAr)]^+$ $[OTf]^-$ was generated in the anodic cell equipped with a carbon felt anode and quickly transferred to a microtube reactor (**R1**). The resulting solution was then mixed with solution of **2** in a micromixer (**M1**) to obtain products **3** and **4**. The flow rate was altered to change the electrolysis time. The trial with a flow rate of 0.6 mL/min gave a moderate yield, even at 0 °C (Table 2, entry 1). As the flow rate was gradually increased to 3.0 mL/min, which led shortening of the electrolysis time, a significant increase in the yield was observed (Table 2, entries 2-4). Notably, an almost quantitative yield was obtained at 3.0 mL/min and the electrolysis time was 8 seconds. In addition, although there seemed to be a slight decrease in the generation efficiency of $[ArS(ArSSAr)]^+$ $[OTf]^-$, the target products were obtained in good yields even at higher flow rates (Table 2, entries 5 and 6). These results clearly shows that flash electrolysis in the flow electrochemical reactor is effective for using highly unstable $[ArS(ArSSAr)]^+$ $[OTf]^-$.

Table 2. Flash Generation and Reaction of $[ArS(ArSSAr)]^+$ $[OTf]^-$ in a Flow Electrochemical Reactor System.



entry	flow rate [mL/min]	electrolysis time [s]	yield of **3** [%][a]	yield of **4** [%][a]
1	0.6	42	59	5
2	1.0	25	84	4
3	2.0	13	91	3
4	3.0	8	96	1
5	4.0	6	90	1
6	5.0	5	86	0

Conditions: **1** (0.05 M in Bu_4NOTf/CH_2Cl_2), TfOH (0.05 M in Bu_4NOTf/CH_2Cl_2), **2** (0.34 M in CH_2Cl_2, 5 eq. for $[ArS(ArSSAr)]^+$ $[OTf]^-$), residence time in **R1** = 12 s, residence time in **R2** = 8 s. [a] Determined by GC analysis.

Moreover, $[ArS(ArSSAr)]^+$ $[BF_4]^-$ and $[B(C_6F_5)_4]^-$ were successfully generated with the

same flow setup by changing the supporting electrolytes (Figure 1). Comparing the increase in the yields between 0.6 and 3.0 mL/min, $[ArS(ArSSAr)]^+$ $[OTf]^-$ was more unstable than $[ArS(ArSSAr)]^+$ $[BF_4]^-$. When $Bu_4NB(C_6F_5)_4$ was used as a supporting electrolyte, although almost no significant improvement of yields was observed, $[ArS(ArSSAr)]^+$ with bulky weakly coordinating anions could be utilized in subsequent reactions without cryogenic conditions.

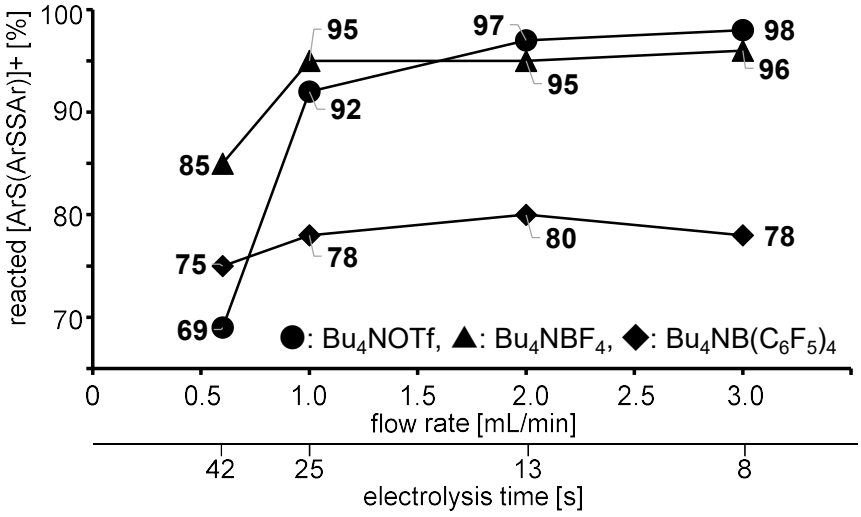
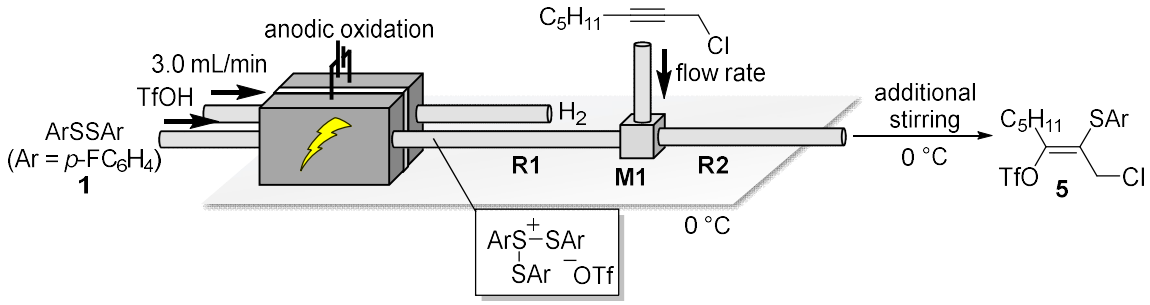


Figure 1. Effect of supporting electrolyte and electrolysis time for generation and reaction of $[ArS(ArSSAr)]^+$.

Next, the reaction of $[ArS(ArSSAr)]^+$ $[OTf]^-$ with alkynes was explored. Electrochemically generated $[ArS(ArSSAr)]^+$ $[BF_4]^-$ (Ar = *p*-FC_6H_4) is known to serve as an efficient thiofluorinating reagent for alkynes.[12] In the reported reaction, $[BF_4]^-$ serves as a fluoride donor. Thus, it is hypothesized that the reaction of $[ArS(ArSSAr)]^+$ $[OTf]^-$ with alkynes could provide vinyl triflates. To confirm the hypothesis, anodically generated $[ArS(ArSSAr)]^+$ $[OTf]^-$ was treated with 1-chloro-2-octyne in the flow setup shown in Table 3, followed by immediate quenching with Et_3N to obtain the desired product **5** in moderate yield (Table 3, entry 1). The E-selectivity of the product indicates that the formation of an episulfonium ion and subsequent anti-addition of $[OTf]^-$ proceeded as previously reported.[12,13] Notably, the reaction with the unsymmetrical alkyne with a chloromethyl group led to the formation of a single regioisomer, presumably because the selective nucleophilic attack of $[OTf]^-$ occurred at the position where a more stable cation was generated due to the electron donating property of the long alkyl chain. Next, decreasing the inner diameter of the micromixer **M1** resulted in a better yield, indicating efficient mixing promotes the smooth formation of episulfonium ions (Table 3, entry 2).

When the amount of $[ArS(ArSSAr)]^+$ $[OTf]^-$ increased, a slight improvement in the yield was observed (Table 3, entry 3). Moreover, the increase in the reaction time after mixing in **M1** resulted in improved yields (Table 3, entries 4 and 5), presumably because the nucleophilic attack of $[OTf]^-$ was slower than the formation of episulfonium ions.

Table 3. Thiotriflation of Alkynes Using a Flow Electrochemical Reactor System.

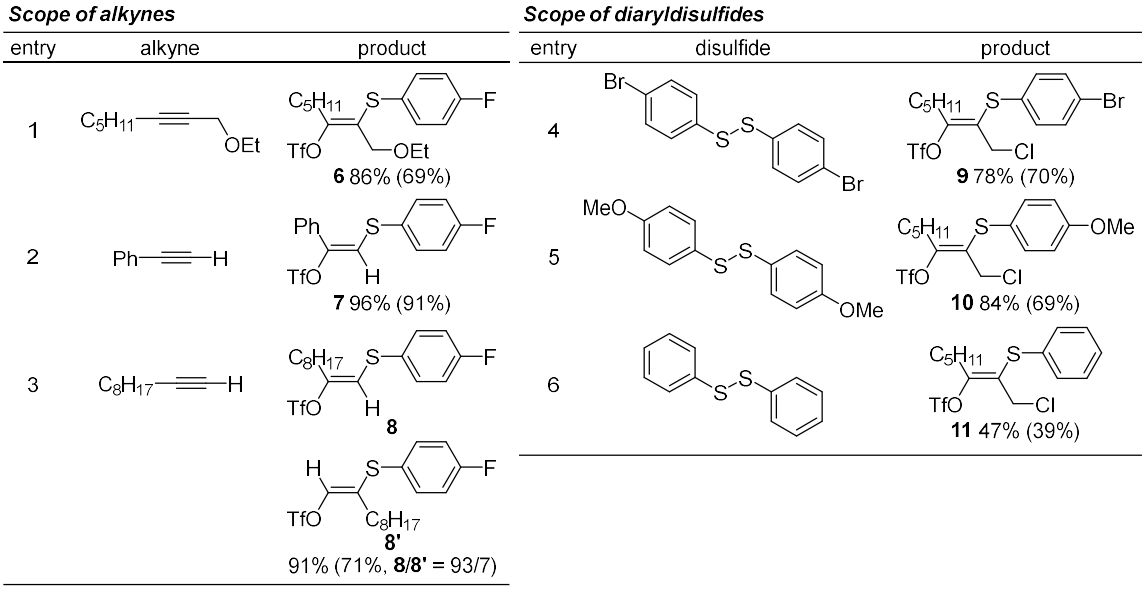


entry	flow rate [mL/min]	equivalents of $[ArS(ArSSAr)]^+$ $[OTf]^-$	inner diameter of **M1** [μm]	additional stirring [min]	yield of **5** [%][a]
1	1.5	1.5	1000	0	57
2	1.5	1.5	500	0	63
3	1.3	1.7	500	0	69
4	1.3	1.7	500	1	74
5	1.3	1.7	500	30	80 (64)[b]

Conditions: **1** (0.05 M in Bu_4NOTf/CH_2Cl_2, 3.0 mL/min), TfOH (0.05 M in Bu_4NOTf/CH_2Cl_2, 3.0 mL/min), alkyne (0.045 M in CH_2Cl_2), residence time in **R1** = 8 s. [a] Determined by ^1H NMR. [b] Yield of the isolated compound.

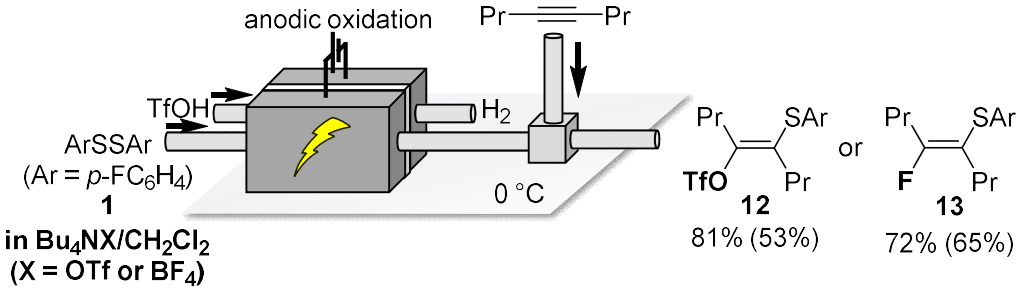
With the standard condition in hand, the scope was investigated (Table 4). Various unsymmetrical alkynes were converted to the corresponding vinyl triflates **6-8** in good to excellent yields with high regioselectvity (Table 4, entries 1-3). Next, scope of diaryldisulfides was investigated; *p*-bromo and *p*-methoxy diaryldisulfide gave the desired products **9** and **10** in good yields (Table 4, entries 4 and 5). When diphenyldisulfide was used, the yield of **11** was relatively low because the undesired oligomerization of the generated sulfonium triflate with the substrate itself (Table 4, entry 6). In addition, switching the product between the vinyl triflate **12** and the vinyl fluoride **13** was feasible by exchanging supporting electrolyte, showing the applicability of this methodology to various alkyne difunctionalization (Scheme 1).

Table 4. Reactions of Anodically Generated $[ArS(ArSSAr)]^+$ $[OTf]^-$ with Alkynes.



Reactions were performed on a 0.07-0.34 mmol scale based on the alkynes. Yields are determined by ^1H NMR, and the numbers in parentheses are the isolated yields.

Scheme 1. Reaction Switching by Exchanging Supporting Electrolyte.



Having confirmed that $[ArS(ArSSAr)]^+$ $[OTf]^-$ serves as an useful building block, an approach to more unstable organic triflates using this sulfonium triflate was investigated. It was reported that $[ArS(ArSSAr)]^+$ $[BF_4]^-$ quickly activates thioacetals,[9] dithioacetals,[14] and *N*,*S*-acetals,[15] allowing to generate the corresponding carbocations. Thus, to generate oxocarbenium triflate, an integrated flow electrochemical reactor system was designed (Figure 2). For the integrated flow system, $[ArS(ArSSAr)]^+$ $[OTf]^-$ and a thioacetal **14** in CH_2Cl_2 was mixed in **M1** to generate oxocarbenium triflate, which was reacted with enol silyl ether as a carbon nucleophile in **M2** to afford the corresponding coupling product **15**.

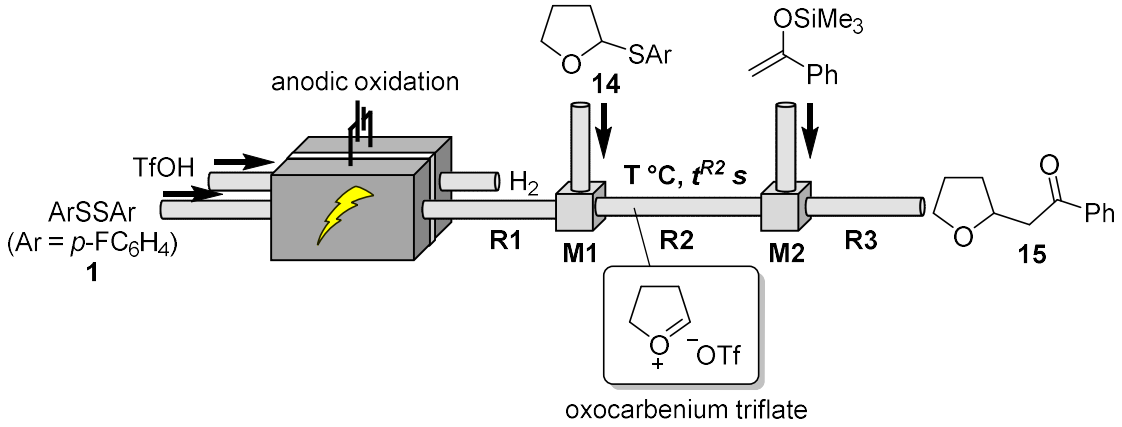


Figure 2. Sequential generation of $[ArS(ArSSAr)]^+$ $[OTf]^-$ and oxocarbenium triflate in an integrated flow electrochemical reactor system.

The reaction was performed by varying temperature T and residence time in **R2** (t^{R2}) to evaluate the stability of oxocarbenium triflate. The yields of **15** were plotted against temperature and t^{R2} as a contour map with scattered overlays (Figure 3). The map indicates that the yields depend significantly on the temperature and residence time in **R2**. At −75 °C, although a significant amount of **14** was recovered in short residence times (e.g., 0.37 and 1.3 s), an increase in t^{R2} resulted in an increase in the conversion of **14**, giving **15** in 93% yield at a t^{R2} of 5.2 s. However, a further increase in t^{R2} caused a decrease in yield, suggesting the high instability of the oxocarbenium triflate. At −50 °C, faster increases and decreases in yield were observed, which suggested faster generation and decomposition of the intermediate. In contrast, the reaction at −25 °C or higher resulted in much lower yields, indicating the quick decomposition of almost all cations. In a series of this study, oligomerized byproducts were detected under low yield conditions by ESI-MS, indicating that a β-elimination of the intermediate and addition reaction with the remaining one occurred as a side reaction.

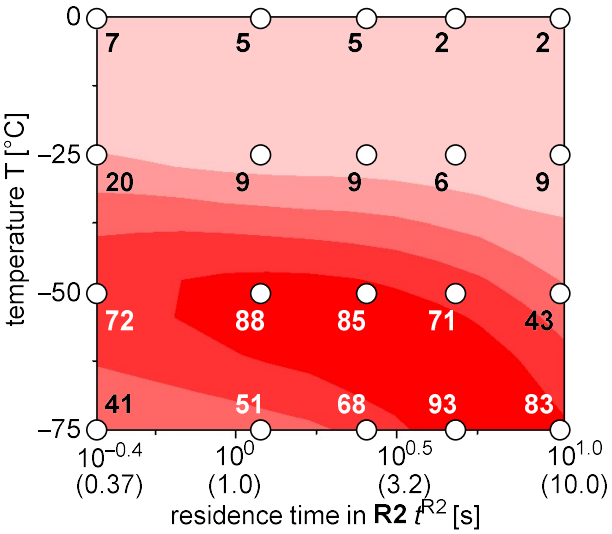


Figure 3. Effect of temperature (T) and residence time in **R2** (t^{R2}) on the yields of **15** using Bu_4NOTf as a supporting electrolyte.

Similar evaluations were carried out by using Bu_4NBF_4 and $Bu_4NB(C_6F_5)_4$ as a supporting electrolyte (Figure 4). The resulting maps provided the suggestion for the relative reactivity of sulfonium ions and the stability of oxocarbenium ions. $[ArS(ArSSAr)]^+$ $[OTf]^-$ activated thioacetal **14** faster than $[ArS(ArSSAr)]^+$ $[BF_4]^-$ and the oxocarbenium triflate decomposed more quickly (Figure 3 and Figure 4 (a)). In addition, the reaction through oxocarbenium ion with $[B(C_6F_5)_4]^-$ resulted in much lower yields even at −50 °C, indicating its extreme instability (Figure 4 (b)).

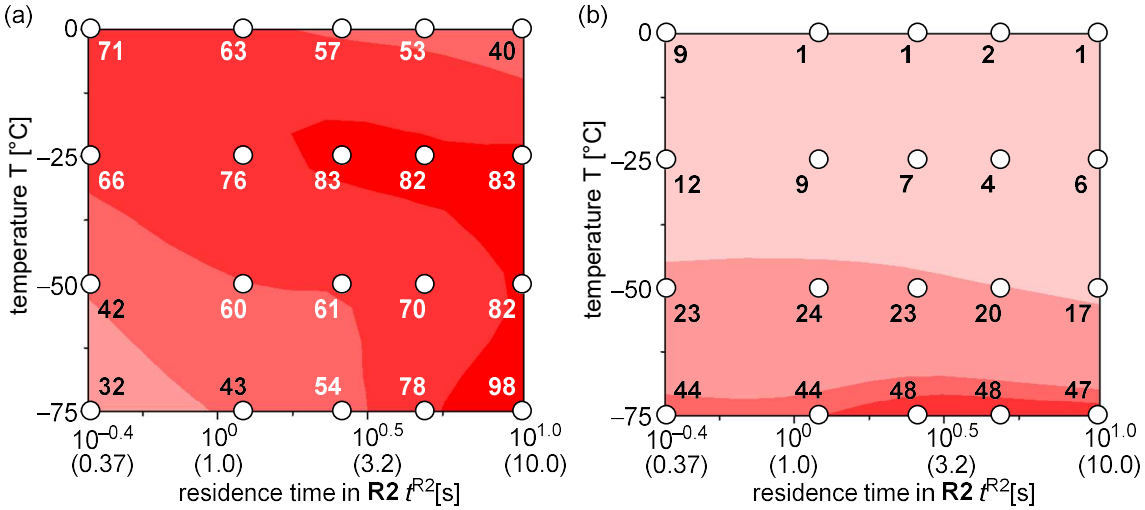
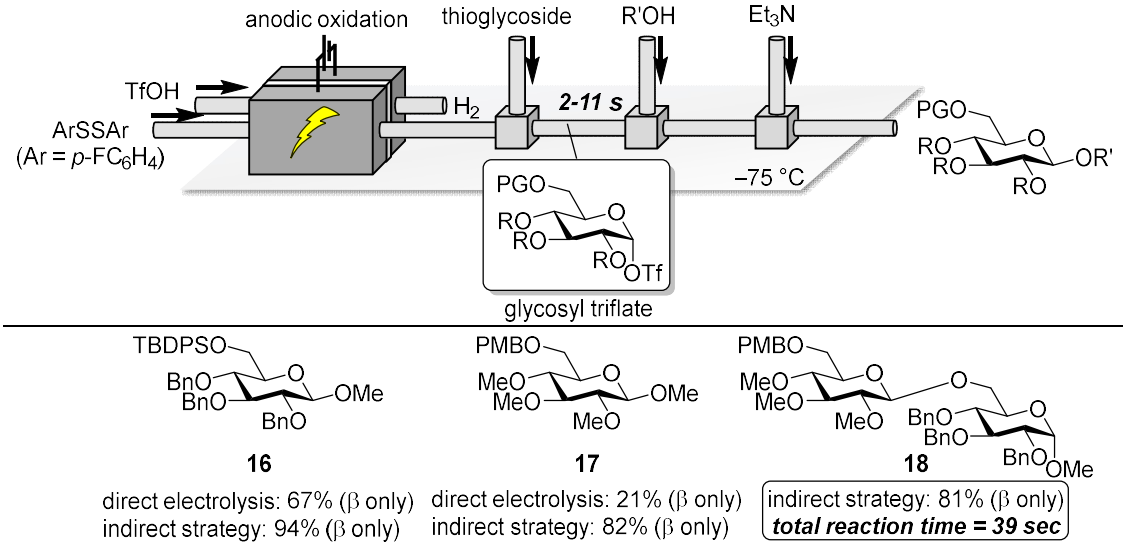


Figure 4. Temperature-residence time maps for generation and reaction of oxocarbenium ions using (a) Bu_4NBF_4 and (b) $Bu_4NB(C_6F_5)_4$ as a supporting electrolyte.

To expand the synthetic utility of this indirect method, application to glycosylation reactions was investigated. In the cation pool method, the direct electrochemical oxidation of thioglycosides in the presence of Bu_4NOTf enables the generation and accumulation of glycosyl triflates.[8] In those reports, although simple protecting groups such as methyl, acetyl, and benzyl groups were mainly employed for glycosyl donors, some useful protecting groups, such as silyl protecting groups and oxidatively labile PMB (*p*-methoxybenzyl), did not survive.[16] Thus, it seems to be reasonable that present non-oxidative activation strategy would achieve efficient and rapid glycosylation without the deprotection of these protecting groups. Before applying this strategy, the direct electrolysis in the flow electrochemical reactor was investigated. Direct anodic oxidation of thioglycosides bearing *tert*-butyldiphenylsilyl (TBDPS) or PMB group in Bu_4NOTf/CH_2Cl_2 system and the subsequent glycosylation with MeOH gave unsatisfactory yields (Scheme 2, **16** and **17**, direct electrolysis). When the indirect strategy was applied, the desired products were obtained in good to excellent yields without deprotection, clearly demonstrating the advantage of this strategy (Scheme 2, **16** and **17**, indirect strategy). Finally, a sequence of electrochemical generation of $[ArS(ArSSAr)]^+$ $[OTf]^-$, indirect generation of glycosyl triflate bearing a PMB group followed by reaction with a glycosyl acceptor, and quenching with Et_3N was successfully achieved in an integrated flow electrochemical reactor system to afford the desired disaccharide **18** in 81% yield. Notably, the whole reaction process from anodic oxidation to Et_3N quenching completed within 40 s, enabling rapid synthesis that was impossible in batch.

Scheme 2. Rapid Glycosylation via Sequential Generation of $[ArS(ArSSAr)]^+$ $[OTf]^-$ and Glycosyl Triflate in an Integrated Flow Electrochemical Reactor System. PG = protecting group.



Conclusion

In conclusion, a powerful method for utilizing highly unstable organic triflates was developed. The key to the success is the achievement of the flash generation of highly reactive $[ArS(ArSSAr)]^+$ $[OTf]^-$ by extremely fast electrolysis using a flow electrochemical reactor. This enabled direct use of $[ArS(ArSSAr)]^+$ $[OTf]^-$ not only as an efficient thiotriflating reagent for alkynes, but also an activator for sequential generation of short-lived oxocarbenium triflates. Notably, the stability evaluation of cyclic oxocarbenium triflate and rapid glycosylation via glycosyl triflates bearing oxidatively labile protecting groups were successfully demonstrated in the integrated flow system. It is expected that the present flow electrochemical reactor system accelerates the development of organic triflate chemistry.

Experimental Section

General.

^1H, ^{13}C and ^{19}F NMR spectra were recorded on Varian MERCURY plus-400 (^1H: 400 MHz, ^{13}C: 100 MHz, ^{19}F: 377 MHz). Chemical shifts were recorded using TMS (0.0 ppm) or $CDCl_3$ (7.26 ppm) signals for ^1H NMR, $CDCl_3$ (77.0 ppm) for ^{13}C NMR, and benzotrifluoride (−63.2 ppm) for ^{19}F NMR as an internal standard unless otherwise noted. NMR yields were calculated by ^1H NMR analysis with 10 seconds relaxation delay using 1,1,2,2-tetrachloroethane TCE as an internal standard. GC analysis was performed on a Shimadzu GC-2014 gas chromatograph equipped with a flame ionization detector using a fused silica capillary column (Rtx-200; 30 m × 0.25 mm × 0.25 mm). GC yields were calculated by GC analysis using calibration lines derived from commercial or isolated compounds with the internal standards. Mass spectra were recorded on Thermo Fisher Scientific EXACTIVE plus (ESI) or JEOL JMS-700 (EI). Flash chromatography was carried out on a silica gel (Kanto Chem. Co., Silica Gel N, spherical, neutral, 40–100 μm). Gel permeation chromatography (GPC) purification was carried out on a Japan Analytical Industry LC-9201 equipped with JAIGEL-1H and 2H using $CHCl_3$ as eluent. Merck pre-coated silica gel F_{254} plates (thickness 0.25 mm) were used for TLC analyses. Infrared absorption (IR) spectra were recorded on Mettler Toledo ReactIR 15 or SHIMADZU IRSpirit and selected absorption maxima (ν_{max}) were reported in wavenumbers (cm^{-1}). Melting points were recorded on a Yanaco micro melting point apparatus and reported in degrees Celsius. All solution preparations and reactions were carried out in a flame-dried glassware under argon atmosphere using dehydrated solvent unless otherwise noted.

Stainless steel (SUS304) T-shaped micromixer (ϕ = 500 μm) was manufactured by Sanko Seiki Co., Inc. Stainless steel (SUS316) microtube reactors (ϕ = 500 and 1000 μm) were purchased from GL Sciences. PTFE tube (ϕ = 1000 μm) was purchased from ISIS Co., Ltd. The syringe pumps (Harvard Model PHD ULTRA) equipped with gastight syringes (purchased from SGE) were used for introduction of the solutions into the microreactor systems *via* stainless steel fittings (GL Sciences, 1/16 OUW). Reagents were purchased from commercial suppliers and used without further purification unless otherwise noted. Bu_4NBF_4 and Bu_4NOTf were purchased from Sigma-Aldrich and dried at 80 °C/1 mmHg over 12 h before use. $Bu_4NB(C_6F_5)_4$ was synthesized according to the literature procedure[9b] and dried at 80 °C/1 mmHg over 12 h. The supporting electrolyte solution was prepared by dissolving supporting electrolyte (39.5 g for Bu_4NBF_4, 15.7 g for Bu_4NOTf and 36.8 g for $Bu_4NB(C_6F_5)_4$ to 400 mL of dehydrated CH_2Cl_2 (0.3 M for Bu_4NBF_4, 0.1 M for Bu_4NOTf and 0.1 M for $Bu_4NB(C_6F_5)_4$) and was stored over molecular sieves 4A (MS4A). Bis(4-fluorophenyl) disulfide[17], bis(4-methoxyphenyl) disulfide[17], bis(4-bromophenyl) disulfide[17], 1-ethoxy-2-octyne[12], 2-((4-fluorophenyl)thio)tetrahydrofuran[18], 4-fluorophenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside[19] and methyl 2,3,4-tri-*O*-benzyl-α-D-glucopyranoside[20] were synthesized according to the reported procedures.

Preparation of 4-fluorophenyl 2,3,4-tri-*O*-benzyl-6-*O*-((1,1-dimethylethyl)diphenyl-silyl)-1-thio-β-D-glucopyranoside.

To a solution of 4-Fluorophenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (2.30 g, 5.02 mmol) in MeOH (10 mL), was added sodium methoxide (28 wt% in MeOH, 0.2 mL) at room temperature. The mixture was stirred at room temperature for 24 h. Then the solvent was evaporated under reduced pressure and resulting residue was passed through silica plug using ethyl acetate as an eluent and the solvent was removed under reduced pressure to give white solid. The white solid was dissolved in DMF (50 mL), and imidazole (0.68 g, 10.0 mmol) was added. To the solution was added *tert*-butyldiphenylchlorosilane TBDPSCl (2.07g, 7.5 mmol) at 0 °C. The reaction mixture was warmed to room temperature and stirred for 1 h. The reaction was quenched by adding H_2O. After separating and extracting with AcOEt, the organic layer was washed with brine, dried over Na_2SO_4, and the solvent was removed under reduced pressure to give colorless oil. The colorless oil was dissolved in DMF (50 mL) and cooled to 0 °C. To the solution was added NaH (60 wt% dispersion in paraffin liquid, 0.90 g, 22.5 mmol) at the same temperature. After stirring for 1 h, benzyl bromide (3.89 g, 22.7 mmol) was slowly added at 0 °C. Then, the reaction solution was warmed to room temperature and stirred for 12 h. The reaction was quenched by adding sat. NH_4Cl aq. After separating and extracting with ethyl acetate AcOEt, the organic layer was washed with brine, dried over Na_2SO_4, and the solvent was

removed under reduced pressure. The crude product was purified by flash chromatography (hexane/ AcOEt = 10/1) to give the title compound as a colorless syrup (2.5 g, 3.1 mmol, 62% yield). TLC: Rf = 0.54 (hexane/ethyl acetate = 10/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.10 (s, 9H), 3.36-3.40 (m, 1H), 3.51 (t, *J* = 8.0 Hz, 1H), 3.69-3.81 (m, 2H), 3.91-4.01 (m, 2H), 4.61 (d, *J* = 9.7 Hz, 1H), 4.70 (d, *J* = 10.6 Hz, 1H), 4.77 (d, *J* = 10.1 Hz, 1H), 4.85-4.92 (m, 4H), 6.84-6.91 (m, 2H), 7.11-7.17 (m, 2H), 7.23-7.44 (m, 19H), 7.55-7.60 (m, 2H), 7.69-7.73 (m, 2H), 7.75-7.79 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.3, 26.8, 62.6, 75.1, 75.4, 75.9, 77.3 (The peak overlapped with chloroform), 79.9, 80.7, 86.8, 87.7, 115.9 (d, *J* = 22.0 Hz), 127.6, 127.7, 127.8, 127.9, 128.1, 128.4, 128.5, 128.7, 128.8, 129.6, 129.7, 132.9, 133.3, 134.4 (d, *J* = 8.0 Hz), 135.6, 135.8, 137.9, 138.0, 138.2, 162.4 (d, *J* = 247.7 Hz); ^{19}F NMR (377 MHz, $CDCl_3$) δ −114.4-−114.6 (m, 1F); HRMS (ESI) calcd for $C_{49}H_{51}FO_5SSiNa$ [M+Na^+]: 821.3103, found 821.3098; IR ($CHCl_3$ solution) ν_{max}:701, 835, 906, 1081, 1238, 1491, 2032, 2174 cm^{-1}.

Preparation of 4-Fluorophenyl 6-*O*-((4-methoxyphenyl)methyl)-2,3,4-tri-*O*-methyl)-1-thio-β-D-glucopyranoside.

To a solution of 4-Fluorophenyl 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucopyranoside (4.59 g, 10.0 mmol) in MeOH (30 mL), was added sodium methoxide (28 wt% in MeOH, 0.5 mL) at room temperature. The mixture was stirred at room temperature for 24 h and then neutralized by 1.0 M HCl in Et_2O (3.0 mL). The solvent was removed under reduced pressure to give a white solid. The white solid was dissolved in DMF (100 mL) and cooled to 0 ℃. To the solution was added NaH (60 wt% dispersion in paraffin liquid, 1.59 g, 39.8 mmol) at the same temperature. After stirring for 30 min, *p*-methoxybenzyl chloride (2.0 g, 13.0 mmol) was slowly added at 0 ℃. Then, the reaction solution was slowly warmed to room temperature and stirred for 12 h. The reaction was quenched by adding sat. NH_4Cl aq. After separating and extracting with AcOEt, the organic layer was washed with brine, dried over Na_2SO_4, and the solvent was removed under reduced pressure. Then the residue was dissolved in DMF (100 mL) again and cooled to 0 ℃. To the solution was added NaH (60 wt% dispersion in paraffin liquid, 1.80 g, 45.0 mmol) at the same temperature. After stirring for 30 min, methyl iodide (6.38 g, 45.0 mmol) was slowly added at 0 ℃. Then, the reaction solution was slowly warmed to room temperature and stirred for 12 h. The reaction was quenched by adding sat. NH_4Cl aq. After separating and extracting with AcOEt, the organic layer was washed with brine, dried over Na_2SO_4, and the solvent was removed under reduced pressure. The crude product was purified by flash chromatography (hexane/ AcOEt = 2/1) to give the title compound as a white solid (3.1 g, 6.85 mmol, 69% yield). TLC: Rf = 0.37 (hexane/ethyl acetate = 2/1); Melting point: 51-53 ℃; ^{1}H NMR (400 MHz,

$CDCl_3$) δ 2.98-3.03 (m, 1H), 3.12-3.23 (m, 2H), 3.29-3.33 (m, 1H), 3.49 (s, 1H), 3.60 (s, 3H), 3.61-3.66 (m, 1H), 3.64 (s, 3H), 3.70-3.74 (m, 1H), 3.82 (s, 3H), 4.40 (d, J = 9.7 Hz, 1H), 4.50 (pseudo q, J = 11.4 Hz), 6.87-6.93 (m, 4H), 7.24-7.27 (m, 2H), 7.52-7.57 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.3, 60.5, 60.8, 60.9, 68.8, 73.0, 78.8, 79.5, 82.4, 87.2, 88.6, 113.7, 115.8 (d, J = 22.0 Hz), 128.4, 129.2, 130.3, 134.6 (d, J = 8.0 Hz), 159.1, 162.5 (d, J = 247.7 Hz); ^{19}F NMR (377 MHz, $CDCl_3$); δ −114.4- −114.6 (m, 1F); HRMS (ESI) calcd for $C_{23}H_{29}FO_6SNa$ [M+Na^+]: 475.1561, found 475.1570; IR ($CHCl_3$ solution) ν_{max}: 835, 1096, 1252, 1491, 1514, 2200 cm^{-1}.

Electrochemical Generation and Accumulation of [ArS(ArSSAr)]$^+$ [OTf]$^-$ in a Batch Electrochemical Reactor.

The anodic oxidation was carried out using an H-type divided electrochemical cell equipped with a carbon felt anode (Nippon Carbon GF-20-P7, ca 350 mg, dried at 300 ℃/1 mm Hg for 3 h before use) and a platinum plate cathode (Nilaco, 20 mm × 30 mm). A Kikusui PMC350-0.2A was used as a direct current power supply for the electrolysis. In the anodic chamber were placed bis(4-fluorophenyl) disulfide **1** (127 mg, 0.50 mmol) and 0.10 M Bu_4NOTf in CH_2Cl_2 (10 mL). In the cathodic chamber were placed triflic acid (TfOH) (44 μL, 0.50 mmol) and 0.10 M Bu_4NOTf in CH_2Cl_2 (10 mL). The constant current electrolysis (8 mA) was carried out at T ℃ with magnetic stirring until 0.67 F of electricity was consumed (ca. 70 min). After the electrolysis, a solution of 1,3,5-trimethoxybenzene **2** (2.5 M, 1 mL, 2.5 mmol) in CH_2Cl_2 was added to the anodic chamber at T ℃, and the resulting mixture was stirred at T ℃ for 10 min. After addition of triethylamine Et_3N (1 mL) to both chambers, the mixture was warmed to room temperature. The reaction mixture in the anodic chamber was collected and the solvent was removed under reduced pressure. Et_2O was added to the residue and the mixture was analyzed by GC using pentadecane as an internal standard. The results are summarized in Table S1.

Table S1. Electrochemical Generation and Accumulation of [ArS(ArSSAr)]$^+$ [OTf]$^-$ in a Batch Electrochemical Reactor.

entry	temperature T [℃]	yield of **3** [%]	yield of **4** [%]	reacted [ArS(ArSSA)]$^+$ [%][a]	recovered **1** [%]
1	-78	61	0	61	58
2	-50	58	2	62	59
6	0	44	3	50	62

[a] (reacted [ArS(ArSSAr)]$^+$) = (yield of **3**) + (yield of **4**) × 2

(4-Fluorophenyl)(2,4,6-trimethoxyphenyl)sulfane 3.

Electrochemical oxidation (0.67 F/mol) of **1** and subsequent reaction with **2** gave the title compound. The crude was analyzed by GC using pentadecane as an internal standard. GC retention time = 26.5 min; initial oven temperature, 50 ℃ for 5 min; rate of temperature increase, 10 ℃/min; final oven temperature, 300 ℃ for 10 min; white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.81 (s, 6H), 3.86 (s, 3H), 6.20 (s, 2H), 6.83–6.89 (m, 2H), 7.00–7.05 (m, 2H). The NMR spectrum was in a good agreement with the reported one[21].

(2,4,6-Trimethoxy-1,3-phenylene)bis((4-fluorophenyl)sulfane) 4.

Electrochemical oxidation (0.67 F/mol) of **1** and subsequent reaction with **2** gave the title compound. The crude was analyzed by GC using pentadecane as an internal standard. GC retention time = 32.4 min; initial oven temperature, 50 ℃ for 5 min; rate of temperature increase, 10 ℃/min; final oven temperature, 300 ℃ for 10 min; white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.79 (s, 3H), 3.87 (s, 6H), 6.41 (s, 1H), 6.86–6.93 (m, 4H), 7.05–7.11 (m, 4H). The NMR spectrum was in a good agreement with the reported one[21].

Flow Electrochemical Reactor.

The divided-type flow electrochemical reactor is composed of stainless-steel chambers and PTFE plates, formed by a mechanical manufacturing technique at DFC Co., Ltd. Carbon felt for anode (GF-20-P7) was purchased from Nippon Carbon Co., Ltd. and dried at 300 ℃/1 mm Hg for 3 h before use. Pt plate for cathode was purchased from Nilaco Co., Ltd. and the surface was roughened to increase the surface area. Glass filter (Whatman, GF/A) and PTFE membrane (Millipore, pore size is 0.2 μm) for filtration were purchased from commercial suppliers and cut before use. Peltier cooling system was purchased from DFC Co., Ltd. A Kikusui PMC350-0.2A was used as a direct current power supply for the electrolysis.

Flow Setup.

A carbon felt anode (length: 40 mm, width: 10 mm, thickness: 1 mm, weight: ca. 100 mg) and two Pt plates (length: 40 mm, width: 10 mm, thickness: ca. 0.1 mm) were used as anode and cathode respectively. The electrodes were set in the flow channel (channel size; length: 42 mm, width: 10 mm, thickness: 1 mm), and the PTFE layer equipped with diaphragm composed of two glass filters (length: 55 mm, width: 15 mm) and three PTFE membranes (length: 55 mm, width: 15 mm) was inserted between flow channel layers. All components were assembled by four PTFE screws. Microtube reactors were connected to the assembled reactor. The reactor was fixed to the Peltier cooling system by PTFE screws and covered by PTFE plate.

Generation of Arylbis(arylthiol)sulfonium Ions Using Flow Electrochemical Reactor. An electrochemical flow reactor system consisting of a divided flow electrochemical reactor, a T-shaped micromixer (**M1**), two microtube reactors (**R1** and **R2**), and three pre-cooling units (**P1** (L = 200 cm), **P2** (200 cm) and **P3** (100 cm)) was used. The electrochemical reactor was cooled at 0 °C by a Peltier cooling system, and the flow microreactor system was cooled in acetone baths at 0 °C. During the operation, the volume of solution was monitored by sampling the solution and adjusted by changing diameter and length of tube reactor connected to the cathodic chamber. A solution of TfOH (0.05 M in Bu_4NX/CH_2Cl_2, flow rate: F mL/min) was introduced to the cathodic chamber through **P1**. A solution of **1** (0.05 M in Bu_4NX/CH_2Cl_2, flow rate: F mL/min) was introduced to the anodic chamber through **P2**. The constant current electrolysis was carried out at 0 °C. Current value was set to consume 0.67 F/mol of electricity (I mA). The resulting solution from anodic chamber was passed through **R1** (L_1 cm, residence time t^{R1} = 11.8 s) and introduced to **M1** (ϕ = 1000 μm), where a solution of **2** (0.335 M in CH_2Cl_2, flow rate: 1/2F mL/min) was also introduced. The mixed solution was passed through **R2** (L_2 cm, residence time t^{R2} = 7.9 s). After a steady state was reached, the product solution was collected to a vessel containing Et_3N (1 mL). After removing the solvent under reduced pressure, Et_2O and pentadecane were added, and the mixture was analyzed by GC. The experimental parameters and results are summarized in Table S2 and Table S3 respectively.

Table S2. Experimental Parameters for Generation of Arylbis(arylthiol)sulfonium Ions.

entry	flow rate F [mL/min]	electrolysis time [s] [a]	current I [mA]	L_1 [cm]	L_2 [cm]
1	0.6	42.0	32	15	15
2	1.0	25.2	54	25	25
3	2.0	12.6	108	50	50
4	3.0	8.4	162	75	75
5	4.0	6.3	216	100	100
6	5.0	5.0	270	125	125

[a] Calculated from the volume of the anodic flow channel and the flow rate.

Table S3. Generation of Arylbis(arylthiol)sulfonium Ions Using a Flow Electrochemical Reactor System.

entry	supporting electrolyte	flow rate F [mL/min]	yield of **3** [%]	yield of **4** [%]	reacted $[ArS(ArSSA)]^+$ [%][a]	recovered **1** [%]
1	Bu_4NOTf	0.6	59	5	69	66
2	(0.1 M)	1.0	84	4	92	66
3		2.0	91	3	97	67
4		3.0	96	1	98	67
5		4.0	90	1	92	74
6		5.0	86	trace	86	75
7	Bu_4NBF_4	0.6	65	10	85	68
8	(0.3 M)	1.0	85	5	95	66
9		2.0	91	2	95	69
10		3.0	96	0	96	67
11		4.0	95	1	97	65
12		5.0	91	1	93	67
13	$Bu_4NB(C_6F_5)_4$	0.6	63	6	75	65
14	(0.1 M)	1.0	70	4	78	62
15		2.0	72	4	80	63
16		3.0	74	2	78	65
17		4.0	74	2	78	66
18		5.0	74	1	76	66

[a] (reacted $[ArS(ArSSAr)]^+$) = (yield of **3**) + (yield of **4**) × 2

Investigation of Standard Condition for Reactions of Anodically Generated $[ArS(ArSSAr)]^+$ $[OTf]^-$ with Alkynes.

An electrochemical flow reactor system consisting of a divided flow electrochemical reactor, a T-shaped micromixer (**M1**), two microtube reactors (**R1** and **R2**), and three pre-cooling units (**P1** (L = 200 cm), **P2** (200 cm) and **P3** (100 cm)) was used. The electrochemical reactor was cooled at 0 °C by a Peltier cooling system, and the flow microreactor system was cooled in acetone baths at 0 °C. During the operation, the volume of solution was monitored by sampling the solution and adjusted by changing diameter and length of tube reactor connected to the cathodic chamber. A solution of TfOH (0.05 M in 0.1M Bu_4NOTf/CH_2Cl_2, flow rate: 3.0 mL/min) was introduced to the cathodic chamber through **P1**. A solution of **1** (0.05 M in 0.1M Bu_4NOTf/CH_2Cl_2, flow rate: 3.0 mL/min) was introduced to the anodic chamber through **P2**. The constant current electrolysis was carried

out at 0 °C. Current value was set to consume 0.67 F/mol of electricity (162 mA). The resulting solution from anodic chamber was passed through **R1** (50 cm, residence time t^{R1} = 7.9 s) and introduced to **M1** (ϕ μm), where a solution of 1-chloro-2-octyne (0.045 M in CH_2Cl_2, flow rate: F mL/min) was also introduced. The mixed solution was passed through **R2** (500 cm, residence time t^{R2} s). After a steady state was reached, the product solution was collected to a flask at 0 °C. The reaction mixture was stirred at 0 °C for *t* min under Ar. Then Et_3N (1 mL) was added, and the solvent was removed under reduced pressure. The residue was dissolved in Et_2O and filtered, and the crude mixture was analyzed by ^1H NMR using TCE as an internal standard. The crude was purified by GPC. The results are summarized in Table S4.

Table S4. Vinyl Triflate Synthesis in a Flow Electrochemical Reactor System.

entry	ϕ [μm]	F [mL/min]	t^{R2} [s]	*t* [min]	yield of **5** [%]
1	1000	1.5	52	0	57
2	500	1.5	52	0	63
3	500	1.3	55	0	69
4	500	1.3	55	1	74
5	500	1.3	55	30	80 (64)[a]

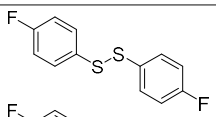
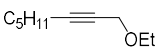
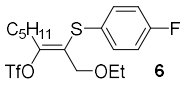
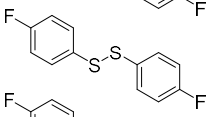
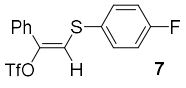
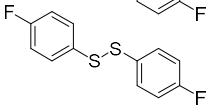
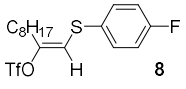
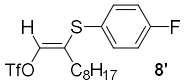
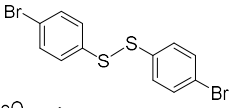
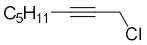
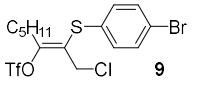
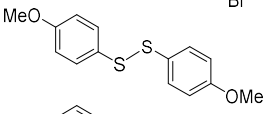
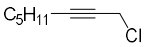
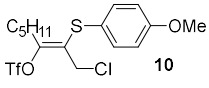
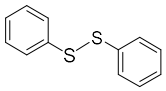
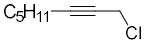
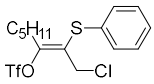
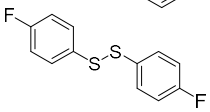
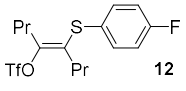
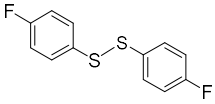
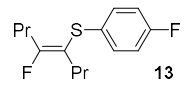
[a] Yield of the isolated compound.

(*E*)-1-Chloro-2-((4-fluorophenyl)thio)oct-2-en-3-yl trifluoromethanesulfonate 5. Electrochemical oxidation (0.67 F/mol) of **1** (0.30 mmol) in Bu_4NOTf/CH_2Cl_2 and subsequent reaction with 1-chloro-2-octyne (0.12 mmol) gave the title compound. The yields were determined by ^1H NMR using TCE as an internal standard and purified by GPC; 31.3 mg, 64% isolated yield, pale yellow oil; ^1H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, *J* = 6.8 Hz, 3H), 1.32-1.38 (m, 4H), 1.62 (quint, *J* = 7.3 Hz, 2H), 2.80 (t, *J* = 7.6 Hz, 2H), 4.09 (s, 2H), 7.04-7.10 (m, 2H), 7.37-7.42 (m,2 H); ^{13}C NMR (100 MHz, $CDCl_3$); δ 13.8, 22.2, 26.3, 30.9, 31.9, 39.8, 116.8 (d, J = 21.9 Hz), 118.3 (q, J = 317.8 Hz) 126.4 (d, J = 3.2 Hz), 127.3, 133.8 (d, J = 8.3 Hz), 152.6, 162.9 (d, *J* = 248.0 Hz); ^{19}F NMR (377 MHz, $CDCl_3$); δ −74.7 (s, 3F), −112.6- −112.7 (m, 1F); HRMS (EI) calcd for $C_{15}H_{17}O_3ClF_4S_2$ 420.0244, found 420.0241; IR (neat) ν_{max}: 1135, 1216, 1418, 1491, 1591, 1636, 2936, 2969 cm^{-1}.

Reactions of Anodically Generated [ArS(ArSSAr)]$^+$ [OTf]$^-$ with Alkynes.

An electrochemical flow reactor system consisting of a divided flow electrochemical reactor, a T-shaped micromixer (**M1**), two microtube reactors (**R1** and **R2**), and three pre-cooling units (**P1** (L = 200 cm), **P2** (200 cm) and **P3** (100 cm)) was used. The electrochemical reactor was cooled at 0 ℃ by a Peltier cooling system, and the flow microreactor system was cooled in acetone baths at 0 ℃. During the operation, the volume of solution was monitored by sampling the solution and adjusted by changing diameter and length of tube reactor connected to the cathodic chamber. A solution of TfOH (0.05 M in Bu_4NOTf/CH_2Cl_2, flow rate: 3.0 mL/min) was introduced to the cathodic chamber through **P1**. A solution of disulfide (0.05 M in Bu_4NOTf/CH_2Cl_2, flow rate: 3.0 mL/min) was introduced to the anodic chamber through **P2**. The constant current electrolysis was carried out at 0 ℃. Current value was set to consume 0.67 F/mol of electricity (162 mA). The resulting solution from anodic chamber was passed through **R1** (50 cm, residence time t^{R1} = 7.9 s) and introduced to **M1** (ϕ = 500 μm), where a solution of alkyne (C_1 M in CH_2Cl_2, flow rate: F mL/min) was also introduced. The mixed solution was passed through **R2** (500 cm, residence time t^{R2} s). After a steady state was reached, the product solution was collected to a flask at 0 ℃. The reaction mixture was stirred at 0 ℃ for 30 min under Ar. Then Et_3N (1 mL) was added, and the solvent was removed under reduced pressure. The residue was dissolved in Et_2O and filtered, and the crude mixture was analyzed by ^1H NMR using TCE as an internal standard. The crude was purified by GPC. The results are summarized in Table S5.

Table S5. Reactions of Anodically Generated $[ArS(ArSSAr)]^+$ $[OTf]^-$ with Alkynes.

entry	disulfide	supporting electrolyte	alkyne	product	yield [%][a]
1		Bu_4NOTf		 **6**	86 (69)
2		Bu_4NOTf		 **7**	96 (91)
3		Bu_4NOTf		 **8**  **8'**	91 (71, **8**/**8'** = 93/7)
4		Bu_4NOTf		 **9**	78 (70)
5		Bu_4NOTf		 **10**	84 (69)
6		Bu_4NOTf		 **11**	47 (39)
7		Bu_4NOTf		 **12**	81 (53)
8		Bu_4NBF_4		 **13**	72 (65)

[a] Determined by ^1H NMR using TCE as an internal standard. The numbers in parentheses are the yield of the isolated compound.

(*E*)-1-Ethoxy-2-((4-fluorophenyl)thio)oct-2-en-3-yl trifluoromethanesulfonate 6.
Electrochemical oxidation (0.67 F/mol) of **1** (0.45 mmol) in Bu_4NOTf/CH_2Cl_2 and subsequent reaction with 1-ethoxy-2-octyne (C_1 = 0.045 M, F = 1.3 mL/min, 0.18 mmol) gave the title compound. The yield was determined by ^1H NMR using TCE as an internal standard and purified by GPC; 52.0 mg, 69% isolated yield, pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, *J* = 7.0 Hz, 3H), 1.14 (t, *J* = 7.0 Hz, 3H), 1.31-1.37 (m, 4H), 1.59 (quint, *J* = 7.5 Hz, 2H), 2.77 (t, *J* = 7.4 Hz, 2H), 3.35 (q, *J* = 6.9 Hz, 2H), 4.03(s, 2H), 7.01-7.06 (m, 2H), 7.35-7.40 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$); δ 13.9, 14.9, 22.2, 26.4, 31.0, 31.9, 65.9, 66.0, 116.4 (q, *J* = 317.8 Hz), 127.5 (d, *J* = 3.1 Hz), 127.6, 133.2 (d, *J* = 8.3 Hz), 152.3, 162.5 (d, *J* = 246.8 Hz); ^{19}F NMR (377 MHz, $CDCl_3$); δ −75.0 (s, 3F), −113.9- −114.1 (m, 1F); HRMS (EI) calcd for $C_{16}H_{20}O_4ClF_3S_2$ 430.0896, found 430.0893; IR (neat) ν_{max}: 1138, 1209, 1417, 1490, 1591, 1643, 2962 cm^{-1}.

(*E*)-2-((4-Fluorophenyl)thio)-1-phenylvinyl trifluoromethanesulfonate 7.

Electrochemical oxidation (0.67 F/mol) of **1** (0.45 mmol) in Bu_4NOTf/CH_2Cl_2 and subsequent reaction with phenylacetylene (C_1 = 0.030 M, F = 1.5 mL/min, 0.135 mmol) gave the title compound. The yield was determined by ^1H NMR using TCE as an internal standard and purified by GPC; 46.5 mg, 91% isolated yield, pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 6.60 (s, 1H), 7.05-7.12 (m, 2H), 7.40-7.52 (m, 6H), 7.58-7.62 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$); δ 116.4 (d, *J* = 22.4 Hz), 118.4 (q, *J* = 320.8 Hz), 121.7, 127.5, 128.6, 128.9 (d, *J* = 3.2 Hz), 130.1, 131.1, 132.9 (d, *J* = 8.4 Hz), 142.7, 162.8 (d, *J* = 249.7 Hz); ^{19}F NMR (377 MHz, $CDCl_3$); δ –74.1 (s, 3F), –112.8- –113.0 (m, 1F); HRMS (EI) calcd for $C_{15}H_{10}F_4O_3S_2$ 378.0007, found 378.0006; IR (neat) ν_{max}: 978, 1138, 1209, 1418, 1491, 1591 cm^{-1}.

(*E*)-1-((4-Fluorophenyl)thio)dec-1-en-2-yl trifluoromethanesulfonate 8 and (*E*)-2-((4-fluorophenyl)thio)dec-1-en-1-yl trifluoromethanesulfonate 8'.

Electrochemical oxidation (0.67 F/mol) of **1** (0.54 mmol) in Bu_4NOTf/CH_2Cl_2 and subsequent reaction with 1-decyne (C_1 = 0.045 M, F = 1.0 mL/min, 0.16 mmol) gave the title compounds as an inseparable mixture. The yield was determined by ^1H NMR using TCE as an internal standard and purified by GPC; 46.5 mg (**8**/**8'** = 93/7), 71% isolated yield, pale yellow oil. ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (**8** and **8'**, t, *J* = 6.8 Hz, 3H), 1.21-1.41 (**8** and **8'**, m, 10H), 1.54-1.65 (**8** and **8'**, m, 2H), 2.23 (**8'**, t, *J* = 7.0 Hz, 2H), 2.56 (t, *J* = 7.5 Hz, 2H), 6.27 (**8**, s, 1H), 6.76 (**8'**, s, 3H), 7.01-7.09 (**8** and **8'**, m, 2H), 7.29-7.35 (**8**, m, 2H), 7.35-7.40 (**8'**, m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$, selected); δ 14.1, 22.6, 25.9, 28.6, 29.1, 31.0, 31.8, 116.5 (d, *J* = 22.4 Hz), 117.8, 118.4 (q, *J* = 320.4 Hz), 128.9 (d, 3.2 Hz), 131.7 (d, *J* = 8.4 Hz), 150.7, 162.3 (d, *J* = 248.1 Hz): 13.8, 22.2, 26.3, 30.9, 31.9, 39.8, 116.6 (d, *J* = 22.2 Hz), 117.9, 118.5 (q, *J* = 318.2 Hz), 128.9 (d, *J* = 3.2 Hz), 131.7 (d, *J* = 7.9 Hz), 134.0-134,1 (m), 150.7, 162.4 (d, *J* = 246.4 Hz); ^{19}F NMR (377 MHz, $CDCl_3$); δ –74.2 (**8'**, s, 3F), –74.4 (**8**, s, 3F), –74.2 (**8'**, s, 3F), –112.59- –113.1 (**8'**, m, 1F), –114.1- –114.4 (**8**, m, 1F); HRMS (EI) calcd for $C_{17}H_{22}O_3F_4S_2$ 414.0947, found 414.0945; IR (neat) ν_{max}: 1142, 1215, 1418, 1491, 1592, 2931 cm^{-1}.

(*E*)-2-((4-Bromophenyl)thio)-1-chlorooct-2-en-3-yl trifluoromethanesulfonate 9.

Electrochemical oxidation (0.67 F/mol) of bis(4-bromophenyl) disulfide (0.45 mmol) in Bu_4NOTf/CH_2Cl_2 and subsequent reaction with1-chloro-2-octyne (C_1 = 0.045 M, F = 1.3 mL/min, 0.15 mmol) gave the title compound. The yield was determined by ^1H NMR using TCE as an internal standard and purified by GPC; 49.1 mg, 70% isolated yield, colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 0.90 (t, *J* = 7.0 Hz, 3H), 1.31-1.37 (m, 4 H), 1.61 (quint, *J* = 7.4 Hz, 2H), 2.78 (t, *J* = 7.6 Hz, 2H), 4.14 (s, 2H), 7.21-7.24 (m, 2H), 7.46-7.50 (m, 2H);

^{13}C NMR (100 MHz, $CDCl_3$); δ 13.8, 22.2, 26.3, 30.9, 31.9, 40.2, 118.3 (q, *J* = 317.8 Hz), 122.2, 126.2, 131.1, 132.0, 132.7, 154.1; ^{19}F NMR (377 MHz, $CDCl_3$); δ −74.6 (s, 3F); HRMS (EI) calcd for $C_{15}H_{17}O_3ClBrF_3S_2$ 479.9443, found 479.9445; IR (neat) ν_{max}: 1135, 1216, 1417, 1472, 1640, 2938 cm^{-1}.

(*E*)-1-Chloro-2-((4-methoxyphenyl)thio)oct-2-en-3-yl trifluoromethanesulfonate 10.
Electrochemical oxidation (0.67 F/mol) of bis(4-mehoxyphenyl) disulfide (0.45 mmol) in Bu_4NOTf/CH_2Cl_2 and subsequent reaction with 1-chloro-2-octyne (C_1 = 0.045 M, F = 1.0 mL/min, 0.14 mmol) gave the title compound. The yield was determined by ^{1}H NMR using TCE as an internal standard and purified by GPC; 40.2 mg, 69% isolated yield, pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.92 (t, *J* = 6.8 Hz, 3H), 1.33-1.39 (m, 4H), 1.62 (quint, *J* = 7.3 Hz, 2H), 2.81 (t, *J* = 7.6 Hz, 2H), 3.82 (s, 3H), 4.04 (s, 2H), 6.87-6.91 (m, 2H), 7.37-7.40 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$); δ 13.9, 22.3, 26.3, 30.9, 31.7, 39.4, 55.4, 115.1, 118.3 (q, *J* = 320.0 Hz), 121.0, 128.4, 134.7, 150.7, 160.3; ^{19}F NMR (377 MHz, $CDCl_3$); δ −74.8 (s, 3F); HRMS (EI) calcd for $C_{16}H_{20}O_4ClF_3S_2$ 432.0444, found 432.0437; IR (neat) ν_{max}: 1135, 1215, 1247, 1418, 1494, 1592, 1636, 2958 cm^{-1}.

(*E*)-1-Chloro-2-(phenylthio)oct-2-en-3-yl trifluoromethanesulfonate 11.
Electrochemical oxidation (0.67 F/mol) of diphenyl disulfide (0.45 mmol) in Bu_4NOTf/CH_2Cl_2 and subsequent reaction with 1-chloro-2-octyne (C_1 = 0.020 M, F = 1.5 mL/min, 0.066 mmol) gave the title compound. The yield was determined by ^{1}H NMR using TCE as an internal standard and purified by GPC; 10.3 mg, 39% isolated yield, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.91 (t, *J* = 6.8 Hz, 3H), 1.32-1.37 (m, 4H), 1.62 (quint, *J* = 7.4 Hz, 2H), 2.81 (t, *J* = 7.6 Hz, 2H), 4.14 (s, 2H), 7.29-7.38 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$); δ 13.8, 22.2, 26.3, 30.9, 31.9, 40.2, 118.3 (q, *J* = 318.2 Hz), 126.8, 128.0, 130.0, 130.7, 131.8, 153.5; ^{19}F NMR (377 MHz, $CDCl_3$); δ −74.7 (s, 3F); HRMS (EI) calcd for $C_{15}H_{18}O_3ClF_3O_3S_2$ 402.0338, found 402.0334; IR (neat) ν_{max}: 1135, 1213, 1249, 1418, 1457, 1477, 1636, 2932, 2963 cm^{-1}.

(*E*)-5-((4-Fluorophenyl)thio)oct-4-en-4-yl trifluoromethanesulfonate 12.
Electrochemical oxidation (0.67 F/mol) of **1** (0.45 mmol) in Bu_4NOTf/CH_2Cl_2 and subsequent reaction with 4-octyne (C_1 = 0.045 M, F = 1.5 mL/min, 0.20 mmol) gave the title compound **12**. The yield was determined by ^{1}H NMR using TCE as an internal standard and purified by GPC; 41.8 mg, 53% isolated yield, pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (t, *J* = 7.6 Hz, 3H), 0.97 (t, *J* = 7.4 Hz, 3H), 1.52 (sext, *J* = 7.4 Hz, 2H), 1.62 (sext, *J* = 7.4 Hz, 2H), 2.22 (t, *J* = 7.8 Hz, 2H), 2.77 (t, *J* = 7.6 Hz, 2H), 7.01-7.05 (m, 2H), 7.27-7.30 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$); δ 13.2, 13.6, 21.0, 21.3, 35.6,

38.9, 116.1 (d, J = 21.8 Hz), 130.07, 130.14 (d, J = 3.2 Hz), 131.4 (d, J = 8.0 Hz), 139.1, 161.8 (d, J = 244.7 Hz); ^{19}F NMR (377 MHz, $CDCl_3$); δ −75.3 (s, 3F), −114.5- −114.7 (m, 1F); HRMS (EI) calcd for $C_{15}H_{18}O_3F_4S_2$ 386.0634, found 386.0633; IR (neat) ν_{max}: 917, 1138, 1209, 1414, 1491, 1592, 1643, 2879, 2971 cm^{-1}.

(*E*)-(5-Fluorooct-4-en-4-yl)(4-fluorophenyl)sulfane 13.

Electrochemical oxidation (0.67 F/mol) of **1** (0.67 mmol) in Bu_4NBF_4/CH_2Cl_2 and subsequent reaction with 4-octyne (C_1 = 0.045 M, F = 1.5 mL/min, 0.34 mmol) gave the title compound. The yield was determined by ^{1}H NMR using TCE as an internal standard and purified by GPC; 56.3 mg, 65% isolated yield, colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.85 (t, J = 7.2 Hz, 3H) and 0.95 (t, J = 7.6 Hz, 3H), 1.48 (sext, J = 7.4 Hz, 2H), 1.59 (sext, J = 7.1 Hz, 2H), 2.18 (td, J = 7.4, 3.2 Hz, 2H), 2.62 (dt, J = 23.2, 7.4 Hz, 2H), 6.94-7.01 (m, 2H), 7.17-7.23 (m, 2H). The NMR spectrum was in a good agreement with the reported one[12].

Generation of Oxocarbenium Ions Using Integrated Flow Electrochemical Reactor System.

An integrated flow electrochemical reactor system consisting of a divided flow electrochemical reactor, a T-shaped micromixers (**M1** and **M2**), three microtube reactors (**R1**, **R2** and **R3**), and four pre-cooling units (**P1** (L = 200 cm), **P2** (200 cm), **P3** (100 cm) and **P4** (100 cm)) was used. The electrochemical reactor was cooled at T_1 ℃ by a Peltier cooling system, and the flow microreactor system was cooled at T_2 ℃ in acetone baths. During the operation, the volume of solution was monitored by sampling the solution and adjusted by changing diameter and length of tube reactor connected to the cathodic chamber. A solution of TfOH (0.05 M in Bu_4NX/CH_2Cl_2, flow rate: 3.0 mL/min) was introduced to the cathodic chamber through **P1**. A solution of **1** (0.05 M in Bu_4NX/CH_2Cl_2, flow rate: 3.0 mL/min) was introduced to the anodic chamber through **P2**. The constant current electrolysis was carried out at T_1 ℃. Current value was set to consume 0.67 F/mol of electricity (162 mA). The resulting solution from anodic chamber was passed through **R1** (L_1 cm) and introduced to **M1** (ϕ = 500 μm), where a solution of **14** (C_1 M in CH_2Cl_2, flow rate: 1.5 mL/min) was also introduced. The mixed solution was passed through **R2** (L_2 cm, residence time t^{R2} s). The resulting solution was introduced to **M2** (ϕ = 500 μm), where a solution of enol silyl ether (C_2 M in CH_2Cl_2, flow rate: 1.5 mL/min) was also introduced. The mixed solution was passed through **R3** (L_3 = 100 cm, residence time t^{R3} = 7.9 s). After a steady state was reached, the product solution was collected and stirred at room temperature for 30 min. After addition of Et_3N (1 mL) to the mixture, the solvent was

removed under reduced pressure. To the crude, Et_2O and pentadecane were added, and the mixture was analyzed by GC. The experimental parameters and results are summarized in Table S6 and Table S7-S9 respectively.

Table S6. Experimental Parameters for Generation of Oxocarbenium Ions.

entry	supporting electrolyte	L_1 [cm]	L_2 [cm]	t^{R2} [s]
1	Bu_4NOTf or	15	3.5	0.37
2	Bu_4NBF_4	15	12.5	1.3
3		15	25	2.6
4		15	50	5.2
5		15	100	10.5
6	$Bu_4NB(C_6F_5)_4$	65	3.5	0.37
7		65	12.5	1.3
8		65	25	2.6
9		65	50	5.2
10		65	100	10.5

Table S7. Generation of Oxocarbenium Triflate Using Bu_4NOTf.

entry	supporting electrolyte	C_1 [M]	C_2 [M]	T_1 [°C]	T_2 [°C]	t^{R2} [s]	conversion of **14** [%]	Yield of **15** [%]
1	Bu_4NOTf	0.045	0.225	0	0	0.37	99	7
2	(0.1 M)					1.3	98	5
3						2.6	100	5
4						5.2	100	2
5						10.5	99	2
6		0.045	0.225	–25	–25	0.37	83	20
7						1.3	100	9
8						2.6	100	9
9						5.2	100	6
10						10.5	99	9
11		0.045	0.225	–50	–50	0.37	75	72
12						1.3	88	88
13						2.6	>99	85
14						5.2	>99	71
15						10.5	>99	43

16		0.045	0.225	–75	–75	0.37	74	41
17						1.3	88	51
18						2.6	95	68
19						5.2	95	93
20						10.5	>99	83

Table S8. Generation of Oxocarbenium Ions Using Bu_4NBF_4.

entry	supporting electrolyte	C_1 [M]	C_2 [M]	T_1 [°C]	T_2 [°C]	t^{R2} [s]	conversion of **14** [%]	Yield of **15** [%]
1	Bu_4NBF_4	0.045	0.225	0	0	0.37	>99	71
2	(0.3 M)					1.3	>99	63
3						2.6	>99	57
4						5.2	>99	53
5						10.5	>99	40
6		0.045	0.225	–25	–25	0.37	88	66
7						1.3	92	76
8						2.6	>99	83
9						5.2	>99	82
10						10.5	>99	83
11		0.045	0.225	–50	–50	0.37	57	42
12						1.3	71	60
13						2.6	81	61
14						5.2	90	70
15						10.5	>99	82
16		0.045	0.225	–75	–75	0.37	49	32
17						1.3	63	43
18						2.6	73	54
19						5.2	80	78
20						10.5	>99	98

Table S9. Generation of Oxocarbenium Ions Using $Bu_4NB(C_6F_5)_4$.

entry	supporting electrolyte	C_1 [M]	C_2 [M]	T_1 [°C]	T_2 [°C]	t^{R2} [s]	conversion of **14** [%]	Yield of **15** [%]
1	$Bu_4NB(C_6F_5)_4$	0.031	0.155	0	0	0.37	99	9
2	(0.1 M)					1.3	99	1

3					2.6	99	1
4					5.2	97	2
5					10.5	99	1
6	0.031	0.155	0	–25	0.37	96	12
7					1.3	99	9
8					2.6	99	7
9					5.2	99	4
10					10.5	99	6
11	0.031	0.155	0	–50	0.37	97	23
12					1.3	97	24
13					2.6	98	23
14					5.2	98	20
15					10.5	99	17
16	0.031	0.155	0	–75	0.37	94	44
17					1.3	94	44
18					2.6	96	48
19					5.2	96	48
20					10.5	97	47

1-Phenyl-2-(tetrahydro-2-furanyl)ethenone 15.

Electrochemical oxidation (0.67 F/mol) of **1**, subsequent treatment with **14**, followed by the reaction with 1-phenyl-1-(trimethylsilyloxy)ethylene gave the title compound. The crude was analyzed by GC using pentadecane as an internal standard. GC retention time = 20.9 min; initial oven temperature, 50 °C for 5 min; rate of temperature increase, 10 °C/min.; pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ1.54 (m, 1H), 1.93 (m, 2H), 2.20 (m, 1H), 3.06 (dd, J_1 = 6.8 Hz, J_2 = 9.6 Hz, 1H), 3.40 (dd, J_1 = 6.4 Hz, J_2 = 10.0 Hz, 1H), 3.76 (q, J = 7.2 Hz, 1H), 3.90 (q, J = 7.2 Hz, 1H), 4.41 (m, 1H), 7.47 (t, J = 7.2 Hz, 2H), 7.57 (t, J = 7.6 Hz, 1H), 7.94 (d, J = 6.4 Hz, 2H). The NMR spectrum was in a good agreement with the reported one.[22]

Direct Electrooxidative Generation of Glycosyl Triflates Using a Flow Electrochemical Reactor System.

A flow electrochemical reactor system consisting of a divided flow electrochemical reactor, a T-shaped micromixer (**M1**), two microtube reactors (**R1** and **R2**), and three pre-cooling units (**P1** (L = 200 cm), **P2** (200 cm) and **P3** (100 cm)) was used. The electrochemical reactor was cooled at −75 ℃ by a Peltier cooling system, and the flow microreactor system was cooled in acetone baths at −75 ℃. During the operation, the volume of solution was monitored by sampling the solution and adjusted by changing diameter and length of tube reactor connected to the cathodic chamber. A solution of TfOH (0.05 M in 0.1M Bu_4NOTf/CH_2Cl_2, flow rate: 3.0 mL/min) was introduced to the cathodic chamber through **P1**. A solution of thioglycoside (0.02 M in 0.1 M Bu_4NOTf/CH_2Cl_2, flow rate: 3.0 mL/min) was introduced to the anodic chamber through **P2**. The constant current electrolysis was carried out at −75 ℃. Current value was set to consume 1.25 F/mol of electricity (121 mA). The resulting solution from anodic chamber was passed through **R1** (15 cm, residence time t^{R1} = 2.4 s) and introduced to **M1** (ϕ = 500 μm), where a solution of MeOH (0.2 M in CH_2Cl_2, flow rate: 1.5 mL/min) was also introduced. The mixed solution was passed through **R2** (L_2 cm, residence time t^{R2} s). After a steady state was reached, the product solution was collected to a flask at rt. The reaction mixture was stirred at rt for 1 min under Ar. Then Et_3N (2 mL) was added, and the solvent was removed under reduced pressure. The crude was purified by flash chromatography.

Methyl 6-*O*-[(1,1-dimethylethyl)diphenylsilyl]-2,3,4-tris-*O*-(phenylmethyl)-β-D-glucopyranoside 16.

Electrochemical oxidation (1.25 F/mol) of 4-fluorophenyl 2,3,4-tri-*O*-benzyl-6-*O*-(*tert*-butyldiphenylsilyl)-1-thio-β-D-glucopyranoside (0.09 mmol) in Bu_4NOTf/CH_2Cl_2 and subsequent reaction with MeOH (0.2 M in CH_2Cl_2, 0.45 mmol) gave the title compound. L_2 = 175 cm, t^{R2} = 18.3 s. The crude was purified by flash chromatography (hexane/ethyl acetate = 20/1); 42.3 mg, 67% (β only) isolated yield, pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.06 (s, 9H), 3.34 (dt, J_1 = 3.0 Hz, J_2 = 9.7 Hz, 1H), 3.44-3.48 (m,1H), 3.60 (s, 3H), 3.67 (t, J = 9.2 Hz, 1H), 3.78 (t, J = 9.2 Hz, 1H), 3.90-3.99 (m, 2H), 4.33 (d, J = 7.5 Hz, 1H), 4.70 (d, J = 10.6 Hz, 1H), 4.74 (d, J = 11.0 Hz, 1H), 4.82 (d, J = 11.0 Hz, 1H), 4.88-4.98(m, 3H), 7.17-7.46 (m, 21H), 7.69-7.79 (m, 5H). The NMR spectrum was in a good agreement with the reported one.[23]

Methyl 2,3,4-tri-*O*-methyl-6-*O*-((4-methoxyphenyl)methyl)-β-D-glucopyranoside 17.

Electrochemical oxidation (1.25 F/mol) of 4-fluorophenyl 6-*O*-((4-methoxyphenyl)methyl)-2,3,4-tri-*O*-methyl)-1-thio-β-D-glucopyranoside (0.15 mmol) in Bu_4NOTf/CH_2Cl_2 and

subsequent reaction with MeOH (0.2 M in CH_2Cl_2, 0.75 mmol) gave the title compound. L_2 = 75 cm, t^{R2} = 7.9 s. The crude was purified by flash chromatography (hexane/ethyl acetate = 10/1 to 2/1); 11.2 mg, 21% (β only) isolated yield. TLC: Rf = 0.19 (hexane/ethyl acetate = 2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.96-3.02 (m, 1H), 3.14-3.18 (m, 2H), 3.28-3.34 (m,1H), 3.48 (s, 3H), 3.53 (s, 3H), 3.57 (s, 3H), 3.60-3.65 (m, 1H), 3.62 (s, 3H), 3.68-3.72 (m, 1H), 3.80 (s, 3H), 4.14 (d, *J* = 7.9 Hz, 1H), 4.54 (pseudo q, *J* = 11.9 Hz, 2H), 6.87 (d, *J* = 8.8 Hz, 2H), 7.27 (d, *J* = 8.8 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.2, 56.9, 60.3, 60.4, 60.8, 68.6, 73.1, 74.7, 79.5, 83.6, 86.5, 104.1, 113.6, 129.3, 130.3, 159.1; HRMS (ESI) calcd for $C_{18}H_{28}O_7Na$ [M+Na^+]: 379.1727, found 379.1728.

Indirect Generation of Glycosyl Triflates Using an Integrated Flow Electrochemical Reactor System.

An integrated flow electrochemical reactor system consisting of a divided flow electrochemical reactor, a T-shaped micromixers (**M1**, **M2** and **M3**), four microtube reactors (**R1**, **R2**, **R3** and **R4**), and five pre-cooling units (**P1** (L = 200 cm), **P2** (200 cm), **P3** (100 cm), **P4** (100 cm) and **P5** (100 cm)) was used. The electrochemical reactor was cooled at −75 °C by a Peltier cooling system, the pre-cooling units **P1** and **P2** were cooled in an acetone bath at −75 °C and the flow microreactor system composed with **P3-P5**, **R1-R4**, **M1-M3** was cooled in acetone baths at −75 °C. During the operation, the amount of solution was monitored by sampling the solution and adjusted by changing diameter and length of tube reactor connected to the cathodic chamber. A solution of TfOH (0.05 M in 0.1 M Bu_4NOTf/CH_2Cl_2, flow rate: 5.0 mL/min) was introduced to the cathodic chamber through **P1**. A solution of **1** (0.05 M in 0.1 M Bu_4NOTf/CH_2Cl_2, flow rate: 5.0 mL/min) was introduced to the anodic chamber through **P2**. The constant current electrolysis was carried out at −75 °C. Current value was set to consume 0.67 F/mol of electricity (270 mA). The resulting solution from anodic chamber was passed through **R1** (15 cm, t^{R1} = 1 s) and introduced to **M1** (ϕ = 500 μm), where a solution of thioglycoside (0.022 M in CH_2Cl_2) was also introduced (flow rate: 1.5 mL/min). The mixed solution was passed through **R2** (L_2 cm, t^{R2} s). The resulting solution was passed through **R3** (L_3 cm, t^{R3} s) and mas mixed with a CH_2Cl_2 solution of nucleophile (flow rate: 1.5 mL/min). After quenching the reaction by mixing Et_3N (neat, flow rate: 1.5 mL/min) at **M3**, the product solution was passed through **R4** (L_4 = 25 cm) and collected to a vessel. The solvent was removed under reduced pressure. Then, the solution was passed through silica plug using Et_2O as an eluent. After concentration under reduced pressure, the crude was purified by flash chromatography.

Methyl 6-*O*-[(1,1-dimethylethyl)diphenylsilyl]-2,3,4-tris-*O*-(phenylmethyl)-β-D-glucopyranoside 16.

Electrochemical oxidation (0.67 F/mol) of **1** (0.38 mmol), subsequent treatment with 4-fluorophenyl 2,3,4-tri-*O*-benzyl-6-*O*-(*tert*-butyldiphenylsilyl)-1-thio- β-D-glucopyranoside (0.0495 mmol), followed by the reaction with MeOH (1.10 M in CH_2Cl_2, 2.48 mmol) gave the title compound. L_2 = 150 cm, t^{R2} = 10.9 s, L_3 = 100 cm, t^{R3} = 5.9 s. The crude was purified by flash chromatography (hexane/ethyl acetate = 5/1); 32.8 mg, 94% (β only) isolated yield.

Methyl 2,3,4-tri-*O*-methyl-6-*O*-((4-methoxyphenyl)methyl)-β-D-glucopyranoside 17.

Electrochemical oxidation (0.67 F/mol) of **1** (0.75 mmol), subsequent treatment with 4-fluorophenyl 6-*O*-((4-methoxyphenyl)methyl)-2,3,4-tri-*O*-methyl)-1-thio-β-D-glucopyranoside (0.099 mmol), followed by the reaction with MeOH (1.10 M in CH_2Cl_2, 4.95 mmol) gave the title compound. L_2 = 100 cm, t^{R2} = 7.3 s, L_3 = 100 cm, t^{R3} =5.9 s. The crude was purified by flash chromatography (hexane/ethyl acetate = 20/1 to 2/1); 29.0 mg, 82% (β only) isolated yield.

Methyl 2,3,4-tris-*O*-benzyl-6-*O*-(2,3,4-tris-*O*-methyl-6-*O*-((4-methoxyphenyl)methyl)-β-D-glucopyranosyl)-α-D glucopyranoside 18.

Electrochemical oxidation (0.67 F/mol) of **1** (0.75 mmol), subsequent treatment with 4-fluorophenyl 6-*O*-((4-methoxyphenyl)methyl)-2,3,4-tri-*O*-methyl)-1-thio-β-D-glucopyranoside (0.099 mmol), followed by the reaction with methyl 2,3,4-tri-*O*-benzyl-α -D-glucopyranoside (0.22 M in CH_2Cl_2, 0.99 mmol) gave the title compound. L_2 = 25 cm, t^{R2} = 1.8 s, L_3 = 500 cm, t^{R3} = 29.5 s. The crude was purified by flash chromatography (hexane/ethyl acetate = 5/1) and GPC; 63.5 mg, 81% (β only) isolated yield, white solid. TLC: Rf =0.07 (hexane/ethyl acetate = 5/1); Melting point: 66-68 ℃; ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.02-3.16 (m, 3H), 3.26-3.30 (m, 1H), 3.37 (s, 3H), 3.47 (s, 3H), 3.51-3.55 (m, 2H), 3.56-3.62 (m, 1H), 3.58 (s, 3H), 3.60 (s, 3H), 3.66-3.70 (m, 2H), 3.78 (s, 3H), 3.79-3.82 (m, 1H), 3.99 (t, J = 9.2 Hz, 1H), 4.14 (dd, J_1 = 1.8 Hz, J_2 = 10.8 Hz, 1H), 4.21 (d, J = 7.6 Hz, 1H), 4.46-4.55(m, 2H), 4.61 (d, J = 3.4 Hz, 1H), 4.63-4.67 (m, 2H), 4.78-4.83 (m, 2H), 4.89 (d, J = 10.8 Hz, 1H), 4.97 (d, J = 10.8 Hz, 1H), 6.82-6.86 (m, 2H), 7.22-7.37 (m, 17H); ^{13}C NMR (125 MHz, $CDCl_3$) δ55.1, 55.2, 60.4, 60.7, 60.8, 68.3, 68.9, 69.8, 73.0, 73.4, 74.9, 75.0, 75.9, 77.9, 79.7, 79.8, 82.1, 83.5, 86.7, 98.1, 103.5, 113.7, 127.6, 127.7, 127.8, 127.9, 128.07, 128.11, 128.38, 128.40, 128.43, 129.2, 130.4, 138.1, 138.4, 138.7, 159.1; HRMS (ESI) calcd for $C_{45}H_{56}O_{12}Na$ [M+Na$^+$]: 811.3664, found 811.3669; IR ($CHCl_3$ solution) ν_{max}: 1088, 1245, 1364, 1458, 1514, 2166 cm^{-1}.

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Chapter 3

Flash Synthesis and Continuous Production of *C*-Arylglycosides Using a Flow Electrochemical Reactor System

Abstract

A rapid and continuous production of *C*-arylglycosides was achieved by using a flow electrochemical reactor system. Electrochemical oxidation of thioglycosides in Bu_4NBF_4/CH_2Cl_2 followed by the reaction with phenols gave the corresponding *C*-arylglycosides. Features of the flow electrochemical reactor such as large electrode surface-to-volume ratio, narrow interelectrode gap, and high temperature controllability enabled rapid and mild transformation, achieving gram-scale production through 60 min continuous operation.

Introduction

Electrochemistry has received significant attention in recent years among researchers in both academia and industry because it offers an efficient and mild synthetic route to useful compounds.[1] Numerous electrochemical methodologies have been developed to produce valuable compounds, including pharmaceuticals and agrochemicals.[2] The remarkable advantage of this methodology is that electrons serve as traceless redox reagents, reducing hazardous chemicals and enabling an environmentally friendly synthetic process. To promote the implementation of this process into the industrial field, development of scalable electrochemical technology has been necessitated.[3] However, conventional batch electrochemical processes suffer from many challenges in increasing productivity from the laboratory scale to the industrial scale. As the electrochemical reactions proceed at surface of an electrode, the simplest strategy involving an enlargement of the reactor volume is not appropriate, because this often requires an increasing in the distance of the electrodes and causes drastic increase in the cell voltage. Moreover, the drawbacks of batch reactors such as insufficient heat transfer and mixing, and long electrolysis duration due to the low electrode surface-to-volume ratio often prevent scaling-up. For these long-standing issues, the incorporation of electrochemistry into flow chemistry is believed to be a promising solution.[4] Flow technology not only enhances the reproducibility and selectivity of electrochemical reactions due to its excellent temperature controllability and narrow interelectrode gap, but also improves the productivity through mass transfer and continuous operation. In recent years, Baran and co-workers developed numerous elegant electrochemical transformations and extended them to flow productions.[5] In their reports, the developed batch methodologies were smoothly applied to a flow reactor in which electrodes were stacked in parallel, achieving 100 g-scale production. Similarly, many researchers have developed unique flow reactors, and new ones continue to be reported.[6] Among them, a divided-type flow electrochemical reactor described in chapter 1 and 2 is expected to be suitable for scale-up synthesis, because the reactor can significantly reduce the electrolysis time, which is the most time-consuming process in the electrochemistry and subsequent chemical reaction of generated cationic intermediates with trapping reagents is carried out in a highly controlled manner under high flow rate condition.

C-Arylglycosides represent important structural motifs found in various biologically active natural compounds that are relevant for medicinal chemistry.[7] The strong C–C bond between sugar and aromatic moieties increases their stability to hydrolytic enzymes in vivo, and they are therefore considered to be promising therapeutic agents. Because of the potential bioactivity as well as the synthetic challenges, they have attracted considerable interest, and accordingly, various chemical synthetic methodologies have been developed.[8]

Moreover, bioactive studies for compounds that mimic and/or simplify natural scaffolds have also been reported.[9] Despite various chemical approaches toward *C*-arylglycosides have been developed, there are few reports on the use of electrochemical methods and they often require specific structures.[10]

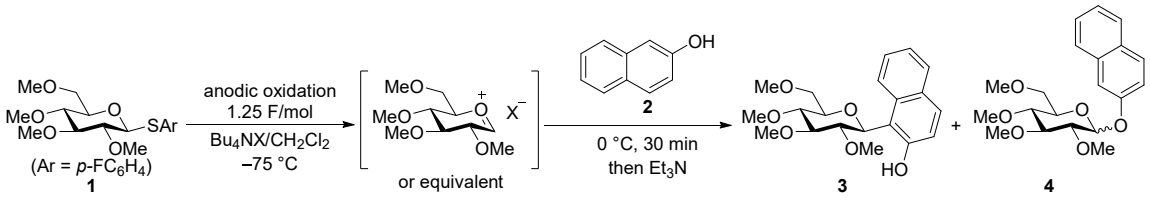
Based on these backgrounds, this chapter describes the rapid and continuous production of *C*-arylglycosides using a flow electrochemical reactor system. In addition to the development of the synthetic method and application to the continuous production in flow, this chapter also includes suggestions on the kinetics of *O*→*C*-glycoside rearrangement.

Results and Discussion

To achieve electrochemical *C*-arylglycoside synthesis, screening of supporting electrolyte was carried out using a divided-type batch electrochemical reactor (Table 1). A solution of thioglycoside **1** containing a supporting electrolyte in CH_2Cl_2 was anodically oxidized at −75 ℃ under a constant current condition until 1.25 F/mol of electricity was consumed. After electrolysis, 5 equivalents of 2-naphthol **2** in CH_2Cl_2 was added, following which the mixture was stirred at 0 ℃ for 30 min and then treated with triethylamine Et_3N to obtain the corresponding products. Target *C*-arylglycoside **3** is a structurally simplified analogue of 8-β-D-glucosylgenistein, and its therapeutic potential has been studied.[9] In the initial trial with Bu_4NOTf, the corresponding *O*-glycoside **4** was obtained in 91% yield (α/β = 80/20) instead of **3** (Table 1, entry 1). In contrast, using $Bu_4NB(C_6F_5)_4$ provided the desired product in a moderate yield (Table 1, entry 2). Applying Bu_4NBF_4/CH_2Cl_2 system allowed to afford the target product with an even better yield (Table 1, entry 3). Note that electrolysis in the presence of **2** gave a lower conversion and yield, presumably because of the undesired oxidation of **2** (Table 1, entry 4).

Having developed an electrochemical method, optimization of the electrolysis temperature was conducted on a larger reaction scale (Table 2). Reaction at −75 ℃ resulted in a slight decrease in the yield compared to the smaller scale (Table 2, entry 1). By applying higher temperatures, the product yields increased (Table 2, entries 2–4) and the desired product **3** was obtained in 82% yield at −25 ℃. Although this transformation was revealed to be suitable at around 0 to −25 ℃, electrolysis at 20 ℃ resulted in a low yield, presumably because the generated intermediate decomposed during electrolysis (Table 2, entry 5).

Table 1. Screening of Supporting Electrolyte for *C*-Arylglycosylation.

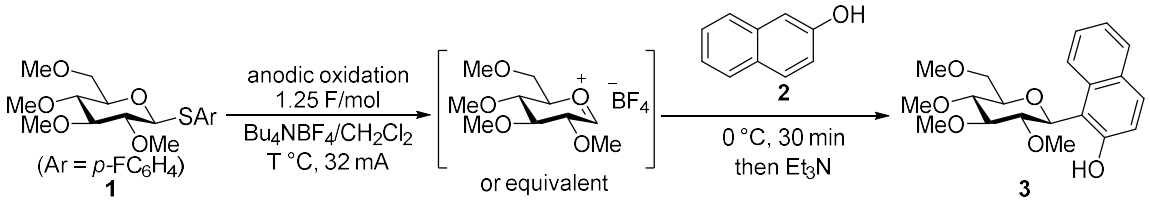


entry	supporting electrolyte	conversion of **1**	yield of **3**	yield of **4**
-	-	[%][a]	[%][a]	[%][a]
1	Bu_4NOTf	>99	0	91[b]
2	$Bu_4NB(C_6F_5)_4$	>99	46	0
3	Bu_4NBF_4	>99	69	0
4[c]	Bu_4NBF_4	53	30	0

Reaction conditions: **1** (0.12 mmol), **2** (0.60 mmol), current = 8 mA, electrolysis time = 30 min.

[a] Determined by ^{1}H NMR. [b] Yields of the isolated compound. [c] Electrolysis was carried out in the presence of **2**.

Table 2. Electrolysis Temperature Optimization.



entry	temperature T	yield of **3**
-	[°C]	[%][a]
1	–75	49
2	–50	64
3	–25	82 (82[b])
4	0	80
5	20	34

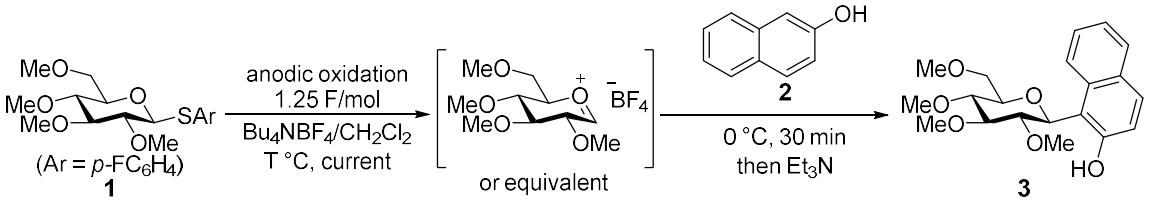
Reaction conditions: **1** (0.50 mmol), current = 32 mA, electrolysis time = 32 min, **2** (1.5 mmol).

[a] Determined by ^{1}H NMR. [b] Yield of the isolated compound.

With the standard conditions in hand, reducing the reaction process time in the batch reactor was investigated. As the present electrochemical conversion is carried out under constant-current conditions, increasing the current decreases the electrolysis time, and thus is expected to improve the productivity. However, when a higher current was applied, significant increase in the cell voltage and decrease in the yield was observed (Table 3, entries 1–4). These results suggested that the heat generated at the anode by the electrical

resistance was not sufficiently removed, causing decomposition of the intermediate. To conduct the transformation in a greener manner, electrolysis was performed with a reduced amount of supporting electrolyte, also resulted in a significant increase in the cell voltage and a further decrease in the yield (Table 3, entries 5–8). These experiments suggest that electrolysis process in batch reactors have unavoidable trade-offs and severe limitations in improving productivity.

Table 3. Effect of Applied Current and Concentration of Supporting Electrolyte in Batch.



entry	concentration of supporting electrolyte	temperature T	current I	electrolysis time	cell voltage	yield of **3**
-	[M]	[°C]	[mA]	[min]	[V]	[%][a]
1	0.3	–25	32	32	20	82(82[b])
2	0.3	–25	200	5	88	69
3	0.3	0	32	32	15	80
4	0.3	0	200	5	74	50
5	0.1	–25	32	32	42	67
6	0.1	–25	200	5	230	64
7	0.1	0	32	32	33	70
8	0.1	0	200	5	160	60

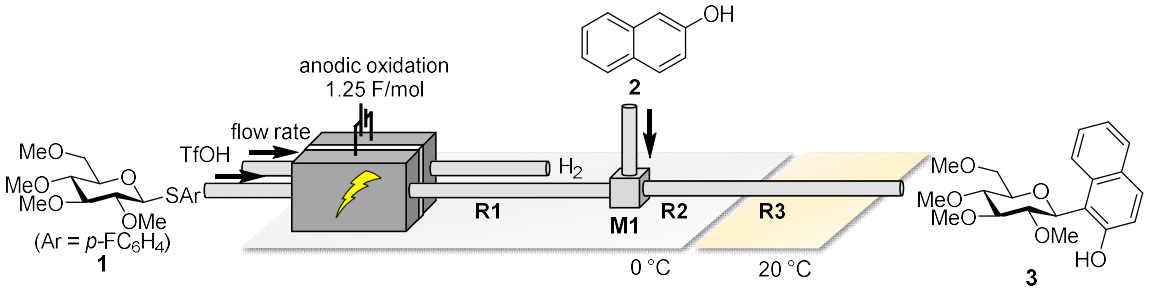
Reaction conditions: **1** (0.50 mmol), **2** (1.5 mmol).

[a] Determined by ^{1}H NMR. [b] Yield of the isolated compound.

To address these issues, the present reaction was applied to a flow electrochemical reactor system described in chapter 1 and 2. In the flow electrochemical reactor, the carbon felt anode and platinum-plated cathode are placed at a distance of 1 mm and divided by a diaphragm composed of glass filters and PTFE membranes. The electrolysis temperature was controlled by a Peltier cooling system. For the flow system, a solution of **1** (0.02 M) containing a supporting electrolyte (Bu_4NBF_4, 0.1 M) in CH_2Cl_2 was introduced by syringe pumping into the anodic chamber. To promote electrolysis, a trifluoromethanesulfonic acid (TfOH) solution (0.05 M) containing the supporting electrolyte (Bu_4NBF_4, 0.1 M) in CH_2Cl_2 was also introduced into a cathodic chamber. Constant-current electrolysis (1.25

F/mol) was performed at 0 °C. The resulting solution in the anodic chamber was quickly transferred to a microtube reactor (**R1**), mixed with nucleophile **2** in a micromixer (**M1**), and reacted through **R2** and **R3** to afford *C*-arylglycoside **3**. To evaluate the performance of the flow system, the reaction was carried out by varying the flow rate, and the results are summarized in Table 4. With a flow rate of 1.0 mL/min, the desired product **3** was afforded in 67% yield (Table 4, entry 1). Next, when the flow rate was gradually increased to 5.0 mL/min with the same setup, the yield slightly improved (Table 4, entries 2–5). Notably, the quantitative conversion of **1** was maintained even at 5.0 mL/min, implying that electrolysis could be accomplished in 5 s. Thus, the increase in the flow rate not only shortened the electrolysis time but also enabled the quick transfer of the intermediate generated in the anodic chamber followed by the immediate reaction with the nucleophile, which contributed to the improved yields and productivity. Furthermore, another attempt to improve productivity by increasing the concentration of **1** was successful, and productivity increased to 2.4 g/h (Table 4, entries 6 and 7). In a series of experiments, excellent temperature controllability of the flow system allowed for steady electrolysis under high-current conditions, e.g., 200 mA, where a drop in the yield was observed in the batch reactor. Moreover, the cell voltage could be kept to a much lower level even at a reduced supporting electrolyte concentration owing to the narrow interelectrode gap. In addition, electrochemical oxidation of thioribofuranoside **5** and subsequent treatment with 4-methoxyphenol gave the corresponding *C*-arylglycoside **6** in good yield, suggesting the generality of the present methodology (Scheme 1).

Table 4. *C*-Arylglycoside Synthesis Using Flow Electrochemical Reactor System.

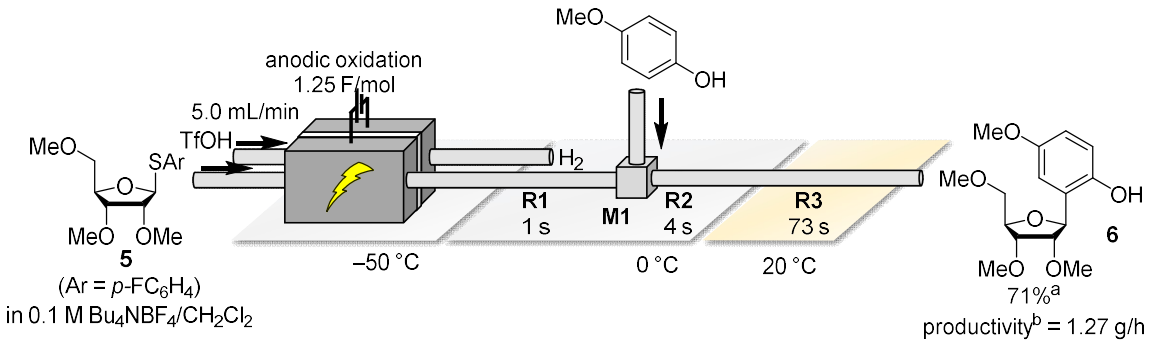


entry	flow rate	current	electrolysis time	cell voltage	conv. of **1**	yield of **3**	calculated productivity
-	[mL/min]	[mA]	[s][a]	[V]	[%][b]	[%][b]	[g/h][c]
1	1.0	40	25	7	>99	67	0.29
2	2.0	80	13	9	>99	71	0.62
3	3.0	120	8	12	>99	71	0.93
4	4.0	160	6	15	>99	73	1.27

5	5.0	200	5	16	>99	73	1.59
6[d]	5.0	250	5	17	>99	69	1.88
7[e]	5.0	300	5	18	>99	74	2.41

[a] Calculated from the volume of the anodic flow channel and the flow rate. [b] Determined by ^{1}H NMR. [c] Calculated from the results of 5 min operation. [d] The reaction was performed at a substrate concentration of 0.025 M. [e] The reaction was performed at a substrate concentration of 0.030 M.

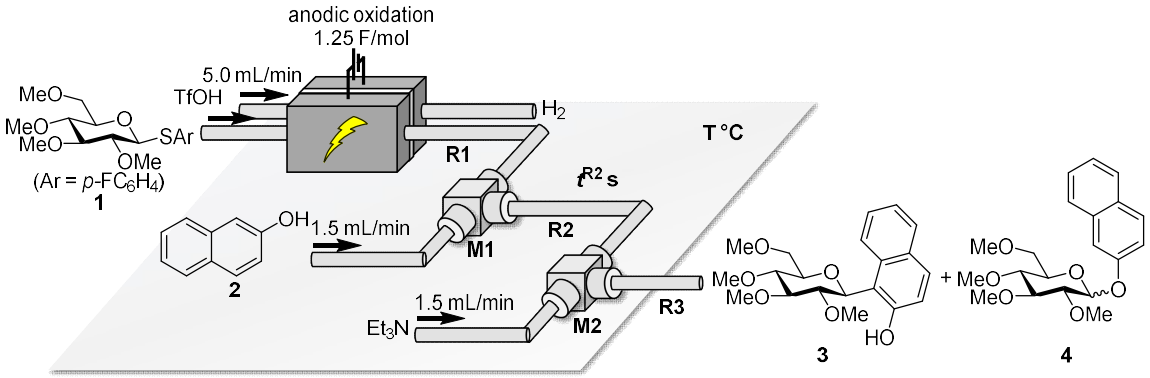
Scheme 1. 5-Membered Ring *C*-Arylglycoside Synthesis Using a Flow Electrochemical Reactor System.



Reaction conditions: thioribofuranoside **5** (0.50 mmol), current = 200 mA, electrolysis time = 5 s, 4-methoxyphenol (1.5 mmol) [a] Yield of the isolated compound. [b] Calculated from the results of 5 min operation.

As a further study, the kinetics of the present transformation was investigated. The reaction was carried out using an integrated flow electrochemical reactor system consisting of two T-shaped micromixers (**M1** and **M2**) and three microtube reactors (**R1**, **R2** and **R3**) shown in Scheme 2 with varying the residence time in **R2** (t^{R2}), and temperature (T). The results are summarized in Figure 1, in which the yields of **3** and **4** are plotted against residence time in **R2**. As shown in Figure 1, it was revealed that *O*-glycoside **4** is initially formed by the reaction of the generated intermediate with nucleophile **2** and *O*-glycoside **4** is converted to *C*-glycoside **3** as the t^{R2} increases. Moreover, the rearrangement of **4** was found to be completed in about 30 s at 20 ℃.

Scheme 2. Kinetic Study of *O*→*C*-Glycoside Rearrangement.



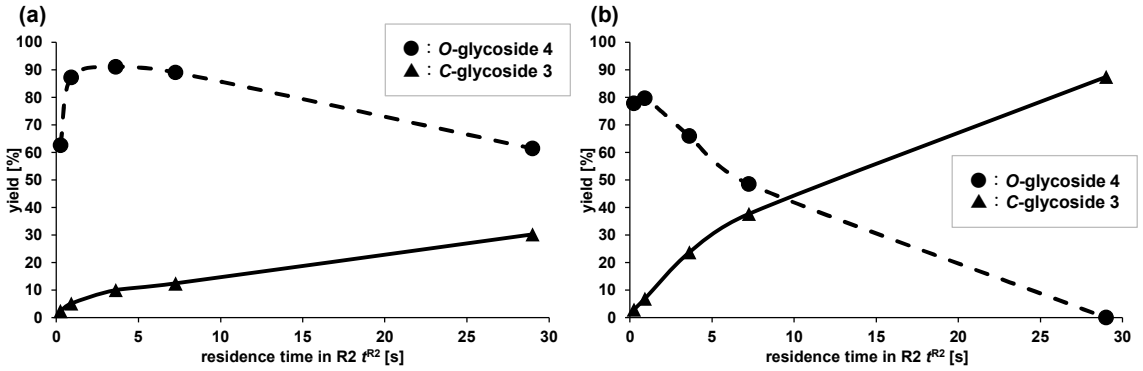
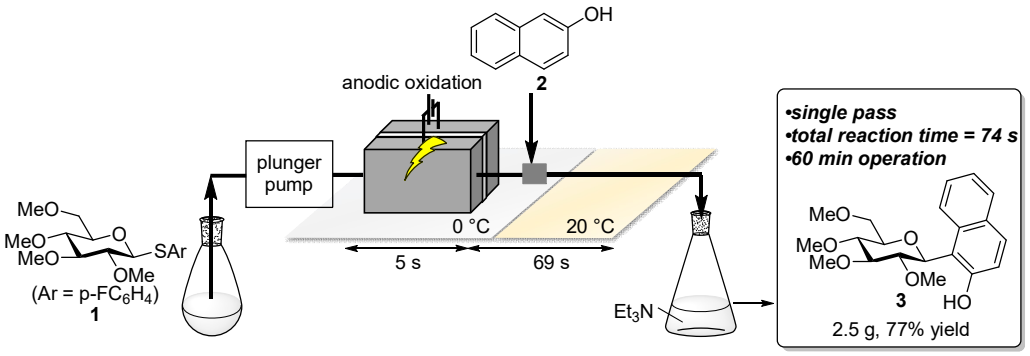


Figure 1. Profile of *O*→*C*-glycoside rearrangement in **R2** (a) at 0 °C; (b) at 20 °C.

Finally, continuous production of **3** was demonstrated by applying plunger pumps to the reactor system instead of syringe pumps (Scheme 3). After 60 min operation, 2.5 g of the desired product was obtained (77% yield). During the operation, the electrolysis temperature was precisely kept at 0 °C, showing the robustness of the system. The overall reaction process in a single passage of the flow system was completed within 75 s, clearly showing the advantage of the flow system in shortening the electrochemical synthesis process.

Scheme 3. Continuous Production of *C*-Arylglycoside **3**.



Conclusion

A simple and efficient *C*-arylglycosylation method involving anodic oxidation of thioglycoside was developed using a batch electrochemical reactor. This method was applied to multi-gram scale continuous production using a flow electrochemical reactor system. The extremely fast electrolysis in the flow electrochemical reactor significantly shortens the electrolysis process and allows rapid synthesis. With the narrow interelectrode gap and the high temperature controllability of the reactor, continuous production at high current conditions was successfully conducted in a controlled manner. Hence the present method adds a new dimension to the organic electrosynthesis and would facilitate the introduction of electrochemistry into the manufacturing process.

Experimental Section

General.

^{1}H and ^{13}C NMR spectra were recorded on Varian MERCURY plus-400 (^{1}H: 400 MHz, ^{13}C: 100 MHz). Chemical shifts are recorded using TMS (0.0 ppm) or $CDCl_3$ (7.26 ppm) signals as an internal standard for ^{1}H NMR, and methin signal of $CDCl_3$ for ^{13}C NMR (77.0 ppm) unless otherwise noted. NMR yields were determined by ^{1}H NMR analyses with 10 seconds relaxation delay using 1,1,2,2-tetrachloroethane (TCE) as an internal standard. Mass spectrum was recorded on Thermo Fisher Scientific EXACTIVE plus (ESI). Infrared absorption (IR) spectrum was recorded on a SHIMADZU IRSpirit and selected absorption maxima (ν_{max}) were reported in wavenumbers (cm^{-1}). Merck pre-coated silica gel F_{254} plates (thickness 0.25 mm) were used for TLC analyses. Flash chromatography was carried out on a silica gel (Kanto Chem. Co., Silica Gel N, spherical, neutral, 40–100 μm). All

solution preparations and reactions were carried out in a flame-dried glassware under argon atmosphere using dehydrated solvent unless otherwise noted. Stainless steel (SUS304) T-shaped micromixer (ϕ = 500 μm) was manufactured by Sanko Seiki Co., Inc. Stainless steel (SUS316) microtube reactors (ϕ = 500 and 1000 μm) was purchased from GL Sciences. PTFE tube (ϕ = 1000 μm) was purchased from ISIS Co., Ltd. The syringe pumps (Harvard Model PHD ULTRA) equipped with gastight syringes (purchased from SGE) were used for introduction of the solutions into the flow electrochemical reactor systems via stainless steel fittings (GL Sciences, 1/16 OUW). The plunger pumps (Shimadzu, LC-20AD) were used for continuous production instead of the syringe pumps. Reagents were purchased from commercial suppliers and used without further purification unless otherwise noted. **1** and **5** were synthesized according to the reported procedure[11]. Bu_4NBF_4 and Bu_4NOTf were purchased from Sigma-Aldrich and dried at 80 ℃/1 mmHg over 12 h before use. $Bu_4NB(C_6F_5)_4$ was synthesized according to the reported procedure[12] and dried at 80 ℃/1 mmHg over 12 h. The supporting electrolyte solution was prepared by dissolving supporting electrolyte (39.5 g for Bu_4NBF_4, 15.7 g for Bu_4NOTf and 18.4 g for $Bu_4NB(C_6F_5)_4$ to 400 mL of dehydrated CH_2Cl_2 (0.3 M for Bu_4NBF_4, 0.1 M for Bu_4NOTf and 0.05 M for $Bu_4NB(C_6F_5)_4$) and stored over molecular sieves 4A (MS4A).

Batch Electrochemical Reactor.

The anodic oxidation was carried out using an H-type divided cell (4G glass filter) equipped with a carbon felt anode (Nippon Carbon GF-20-P7, dried at 300 ℃/1 mm Hg for 3 h before use) and a platinum plate cathode (Nilaco). Kikusui PMC350-0.2A or KENWOOD PA120-0.6B were used as a direct current power supply for the electrolysis. Cell voltages were monitored by KENWOOD dual display multimeter DL-2051.

Screening of Supporting Electrolytes for *C*-Arylglycoside Synthesis Using a Batch Reactor.

In the anodic chamber of a batch electrochemical reactor were placed **1** (0.12 mmol) and supporting electrolyte solution (6 mL). In the cathodic chamber were placed TfOH (27 mm, 0.30 mmol) and supporting electrolyte solution (6 mL). The constant current electrolysis (8 mA) was carried out at −75 ℃ with magnetic stirring until 1.25 F of electricity was consumed (30 min). After the electrolysis, **2** (0.60 mmol) in CH_2Cl_2 (2 mL) was added to the anodic chamber at T ℃, and the resulting mixture was stirred at 0 ℃ for 30 min. After addition of Et_3N (1 mL) to both chambers, the solution was stirred at the same temperature for 10 min. The solution in the anodic chamber was collected and the solvent was removed under reduced pressure. Then, the residue was passed through silica plug using diethyl ether Et_2O as an eluent. After concentration under reduced pressure, the crude mixture was

analyzed by ^{1}H NMR using TCE as an internal standard and purified by flash chromatography. The results are summarized in Table S1.

Table S1. Screening of Supporting Electrolyte for *C*-Arylglycoside Synthesis.

entry	supporting electrolyte	concentration of supporting electrolyte	cell voltage	conversion of **1**	yield of **3**	yield of **4**
-	-	[M]	[V]	[%]	[%]	[%]
1	Bu_4NOTf	0.1	60	>99	0	91[a]
2	$Bu_4NB(C_6F_5)_4$	0.05	116	>99	46	0
3	Bu_4NBF_4	0.3	27	>99	69	0
4[b]	Bu_4NBF_4	0.3	27	53	30	0

[a] Yield of the isolated compound.

[b] Electrolysis was carried out in the presence of the **2**.

1-(2,3,4,6-Tetra-*O*-methyl-β-D-glucopyranosyl)naphthalen-2-ol 3.
Electrochemical oxidation (1.25 F/mol) of 4-fluorophenyl 2,3,4,6-tetra-*O*-methyl-1-thio-β-D-glucopyranoside **1** (0.12 mmol) using Bu_4NBF_4 or $Bu_4NB(C_6F_5)_4$ as a supporting electrolyte and subsequent reaction with 2-naphthol **2** (0.60 mmol) gave the title compound. The aliquot was purified by flash chromatography (hexane/ethyl acetate = 5/1 to 3/1), pale yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.71 (s, 3H), 3.35-3.55 (m, 4H), 3.42 (s, 3H), 3.60-3.67 (m, 2H), 3.62 (s, 3H), 3.68 (s, 3H), 5.25 (d, *J* = 9.7 Hz, 1H), 7.14 (d, *J* = 9.2 Hz, 1H), 7.30 (t, *J* = 7.0 Hz, 1H), 7.44 (t, *J* = 7.0 Hz, 1H), 7.71-7.76 (m, 2H), 7.97 (d, *J* = 8.4 Hz, 1H), 8.52 (s, 1H). The NMR spectrum was in a good agreement with the reported one.[9]

1-(2,3,4,6-Tetra-*O*-methyl-α-D-glucopyranosyl)naphthalen-2-ol 4α and 1-(2,3,4,6-Tetra-*O*-methyl-β-D-glucopyranosyl)naphthalen-2-ol 4β.
Electrochemical oxidation (1.25 F/mol) of 4-fluorophenyl 2,3,4,6-tetra-*O*-methyl-1-thio-β-D-glucopyranoside **1** (0.12 mmol) using Bu_4NOTf as a supporting electrolyte and subsequent reaction with 2-naphthol **2** (0.60 mmol) gave the title compound. The aliquot was purified by flash chromatography (hexane/ethyl acetate = 5/1); 41.2 mg, 91% yield (α/β = 80/20), white solid. ^{1}H NMR (400 MHz, $CDCl_3$) **4α** δ 3.40 (s, 3H), 3.58 (s, 3H), 3.68 (s, 3H), 3.70 (s, 3H), 3.26-3.76 (m, 6H), 4.99 (d, *J* = 7.5 Hz, 1H), 7.22-7.48 (m, 4H), 7.72-7.80 (m, 3H). ^{1}H NMR (400 MHz, $CDCl_3$) **4β** δ 3.38 (s, 3H), 3.54 (s, 3H), 3.58 (s, 3H), 3.73 (s, 3H), 3.26-3.81 (m, 6H), 5.81 (d, *J* = 3.5 Hz, 1H), 7.22-7.52 (m, 4H), 7.72-7.80 (m, 3H). The NMR spectra were in a good agreement with the reported one.[13]

Effect of Electrolysis Temperature, Applied Current and Concentration of Supporting Electrolyte Under Batch Conditions.

In the anodic chamber were placed **1** (0.50 mmol) and supporting electrolyte solution (25 mL). In the cathodic chamber were placed TfOH (110 μL, 1.25 mmol) and supporting electrolyte solution (25 mL). The constant current electrolysis (I mA) was carried out at T °C with magnetic stirring until 1.25 F of electricity was consumed. After the electrolysis, **2** (1.5 mmol) in CH_2Cl_2 (7.5 mL) was added to the anodic chamber at T °C, and the resulting mixture was stirred at 0 °C for 30 min. After addition of Et_3N (1 mL) to both chambers, the solution was stirred at the same temperature for 10 min. The solution in the anodic chamber was collected and the solvent was removed under reduced pressure. Then, the residue was passed through silica plug using Et_2O as an eluent. After concentration under reduced pressure, the crude mixture was analyzed by ^{1}H NMR using TCE as an internal standard and purified by flash chromatography. The results are summarized in Table S2.

Table S2. Effect of Electrolysis Temperature, Applied Current and Concentration of Supporting Electrolyte on the Yield of **3**.

entry	concentration of supporting electrolyte	temperature T	current I	electrolysis time	cell voltage	conv. of **1**	yield of **3**
-	[M]	[°C]	[mA]	[min]	[V]	[%]	[%]
1	0.3	−75	32	32	53	>99	49
2	0.3	−50	32	32	30	98	64
3	0.3	−25	32	32	20	>99	82 (82)[a]
4	0.3	0	32	32	15	>99	80
5	0.3	20	32	32	16	>99	34
6	0.3	−25	200	5	88	98	69
7	0.3	0	200	5	74	99	50
8	0.1	−25	32	32	42	>99	67
9	0.1	−25	200	5	230	>99	64
10	0.1	0	32	32	33	>99	70
11	0.1	0	200	5	160	94	60

[a] Yield of the isolated compound.

Flow Electrochemical Reactor.

The divided-type flow electrochemical reactor is composed of stainless-steel chambers and

PTFE plates, formed by a mechanical manufacturing technique at DFC Co., Ltd. Carbon felt for anode (GF-20-P7) was purchased from Nippon Carbon Co., Ltd. and dried at 300 ℃/1 mm Hg for 3 h before use. Pt plate for cathode was purchased from Nilaco Co., Ltd. and the surface was roughened to increase the surface area. Glass filter (Whatman, GF/A) and PTFE membrane (Millipore, pore size is 0.2 μm) for filtration were purchased from commercial suppliers and cut before use. Peltier cooling system was purchased from DFC Co., Ltd. A KENWOOD PA120-0.6B was used as a direct current power supply for the electrolysis.

Flow Setup.

A carbon felt anode (length: 40 mm, width: 10 mm, thickness: 1 mm, weight: ca. 100 mg) and two Pt plates (length: 40 mm, width: 10 mm, thickness: ca. 0.1 mm) were used as anode and cathode respectively. The electrodes were set in the flow channel (channel size; length: 42 mm, width: 10 mm, thickness: 1 mm), and the PTFE layer equipped with diaphragm composed of two glass filters (length: 55 mm, width: 15 mm) and three PTFE membranes (length: 55 mm, width: 15 mm) was inserted between flow channel layers. All components were assembled by four PTFE screws. Microtube reactors were connected to the assembled reactor. The reactor was fixed to the Peltier cooling system by PTFE screws and covered by PTFE plate.

***C*-Arylglycoside Synthesis Using a Flow Electrochemical Reactor System.**

An electrochemical flow reactor system consisting of a divided electrochemical flow reactor, a T-shaped micromixer (**M1**), three microtube reactors (**R1**, **R2** and **R3**), and three pre-cooling units (**P1** (L = 200 cm), **P2** (200 cm) and **P3** (100 cm)) was used. The electrochemical reactor was cooled at 0 ℃ by a Peltier cooling system, and the flow microreactor system composed of **P1**, **P2**, **P3**, **R1**, **R2** and **M1** was cooled in acetone baths at 0 ℃, and **R3** was warmed in water bath at 20 ℃. During the operation, the amount of solution was monitored by sampling the solution and adjusted by changing diameter and length of tube reactor connected to the cathodic chamber. A solution of TfOH (0.05 M in 0.1 M Bu_4NBF_4/CH_2Cl_2, flow rate: F_1 mL/min) was introduced to the cathodic chamber through **P1**. A solution of **1** (C_1 M in 0.1 M Bu_4NBF_4/CH_2Cl_2, flow rate: F_1 mL/min) was introduced to the anodic chamber through **P2**. The constant current electrolysis was carried out at 0 ℃. Current value (I mA) was set to consume 1.25 F/mol of electricity. The resulting solution from anodic chamber was passed through **R1** (15 cm, residence time t^{R1} s) and introduced to **M1** (ϕ = 500 μm), where a solution of **2** (0.2 M in CH_2Cl_2) was also introduced (flow rate: F_2 mL/min). The mixed solution was passed through **R2** (L_2 cm, residence time t^{R2} s, 0 ℃) and **R3** (L_3 cm, residence time t^{R3} s, 20 ℃). After a steady state

was reached, the product solution was collected to a vessel containing Et_3N (10 mL) for 5 min. After concentration under reduced pressure, the crude solution was passed through silica plug using Et_2O as an eluent to remove supporting electrolyte. After concentration under reduced pressure, the crude mixture was analyzed by ^1H NMR using TCE as an internal standard or purified by flash chromatography. The results are summarized in Table S3.

Table S3. *C*-Arylglycoside Synthesis Using a Flow Electrochemical Reactor System.

entry	concentration of **1** C_1	flow rate F_1	current I	electrolysis time	cell voltage	t^{R1}
-	[M]	[mL/min]	[mA]	[s][a]	[V]	[s]
1	0.020	1.0	40	25	7	7
2	0.020	2.0	80	13	9	4
3	0.020	3.0	120	8	12	2
4	0.020	4.0	160	6	15	1
5	0.020	5.0	200	5	16	1
6	0.025	5.0	250	5	17	1
7	0.030	5.0	300	5	18	1

Table S3. continued

entry	flow rate F_2	**R2** L_2	t^{R2}	**R3** L_3	t^{R3}	conversion of **1**	yield of **3**	calculated productivity
-	[mL/min]	[cm]	[s]	[cm]	[s]	[%]	[%]	[g/h][b]
1	0.3	25	9	200	73	>99	67	0.29
2	0.6	25	5	400	73	>99	71	0.62
3	0.9	50	6	600	73	>99	71	0.93
4	1.2	50	5	800	73	>99	73	1.27
5	1.5	50	4	1000	73	>99	73	1.59
6	1.88	50	3	1000	69	>99	69	1.88
7	2.25	50	3	1000	65	>99	74	2.41

[a] Electrolysis time was calculated from the volume of the anodic flow channel and the flow rate.

[b] Calculated from the results of 5 min operation.

5-Membered Ring *C*-Arylglycoside Synthesis Using a Flow Electrochemical Reactor System.

An electrochemical flow reactor system consisting of a divided electrochemical flow reactor, a T-shaped micromixer (**M1**), three microtube reactors (**R1**, **R2** and **R3**), and three

pre-cooling units (**P1** (L = 200 cm), **P2** (200 cm) and **P3** (100 cm)) was used. The electrochemical reactor was cooled at *T* °C by a Peltier cooling system, and the flow microreactor system composed with **P1**, **P2**, **P3**, **R1**, **R2** and **M1** was cooled in acetone baths, and **R3** was warmed in water bath at 20 °C. During the operation, the amount of solution was monitored by sampling the solution and adjusted by changing diameter and length of tube reactor connected to the cathodic chamber. A solution of TfOH (0.05 M in 0.1 M Bu_4NBF_4/CH_2Cl_2, flow rate: 5.0 mL/min) was introduced to the cathodic chamber through **P1**. A solution of the **5** (0.02 M in 0.1 M Bu_4NBF_4/CH_2Cl_2, flow rate: 5.0 mL/min) was introduced to the anodic chamber through **P2**. The constant current electrolysis was carried out at T °C. Current value was set to consume 1.25 F/mol of electricity (200 mA). The resulting solution from anodic chamber was passed through **R1** (15 cm, t^{R1} = 1.4 s) and introduced to **M1** (ϕ = 500 μm), where a solution of 4-methoxyphenol (0.2 M in CH_2Cl_2, flow rate: 1.5 mL/min) was also introduced. The mixed solution was passed through **R2** (50 cm, residence time t^{R2} = 3.6 s, 0 °C) and **R3** (1000 cm, residence time t^{R3} = 72.5 s, 20 °C). After a steady state was reached, the product solution was collected to a vessel containing Et_3N (3 mL) for 5 min. After concentration under reduced pressure, the crude solution was passed through silica plug using Et_2O as an eluent to remove supporting electrolyte. After concentration under reduced pressure, the crude mixture was analyzed by ^1H NMR using TCE as an internal standard and purified by flash chromatography. The results are summarized in Table S4.

Table S4. 5-Membered Ring *C*-Arylglycoside Synthesis Using a Flow Electrochemical Reactor System.

entry	electrolysis temperature T	cell voltage	conversion of **5**	yield of **6**	calculated productivity
-	[°C]	[V]	[%]	[%][a]	[g/h][b]
1	0	14	>99	49	0.88
2	-50	16	>99	71	1.27

[a] Yield of the isolated compounds

[b] Calculated from the results of 5 min operation.

2-((2*S*,3*S*,4*R*,5*R*)-3,4-Dimethoxy-5-(methoxymethyl)tetrahydrofuran-2-yl)-4-methoxyphenol[14] 6.

Electrochemical oxidation (1.25 F/mol) of **5** (0.5 mmol) using Bu_4NBF_4 as a supporting electrolyte and subsequent reaction with 4-methoxyphenol (1.5 mmol) gave the title

compound. The aliquot was purified by flash chromatography (hexane/ethyl acetate = 5/1 to 2/1); 106.3 mg, 71% yield (β only), pale yellow oil. TLC: Rf = 0.19 (hexane/ethyl acetate = 2/1); ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.36 (s, 3H), 3.46 (s, 3H), 3.48 (s, 3H), 3.58 (dd, J_1 = 2.2 Hz, J_2 = 10.6 Hz, 1H), 3.67 (dd, J_1 = 3.1 Hz, J_2 = 10.1 Hz, 1H), 3.73 (s, 3H), 3.87-3.94 (m, 2H), 4.22-4.25 (m, 1H), 4.86 (d, J = 7.5 Hz, 1H), 6.72-6.83 (m, 3H), 7.42 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.6, 58.0, 58.6, 59.4, 72.4, 78.0, 82.1, 83.3, 83.7, 113.9, 114.8, 117.9, 123.7, 149.1, 152.8; HRMS (ESI) calcd for $C_{15}H_{22}O_6Na$ [M+Na^+]: 321.1309, found 321.1310; IR (neat) ν_{max}: 3388 (br) cm^{-1}.

Kinetic Analysis of the *O*→*C*-Glycoside Rearrangement.

An electrochemical flow reactor system consisting of a divided electrochemical flow reactor, two T-shaped micromixers (**M1** and **M2**), three microtube reactors (**R1**, **R2** and **R3**), and four pre-cooling units (**P1** (L = 200 cm), **P2** (200 cm), **P3** (100 cm) and **P4** (100 cm)) was used. The electrochemical reactor was cooled at 0 °C by a Peltier cooling system, and the flow microreactor system was cooled in an acetone bath or a water bath at T °C. During the operation, the amount of solution was monitored by sampling the solution and adjusted by changing diameter and length of tube reactor connected to the cathodic chamber. A solution of TfOH (0.05 M in 0.1 M Bu_4NBF_4/CH_2Cl_2, flow rate = 5.0 mL/min) was introduced to the cathodic chamber through **P1**. A solution of **1** (0.02 M in 0.1 M Bu_4NBF_4/CH_2Cl_2, flow rate = 5.0 mL/min) was introduced to the anodic chamber through **P2**. The constant current electrolysis was carried out at 0 °C. Current value was set to consume 1.25 F/mol of electricity (200 mA). The resulting solution from anodic chamber was passed through **R1** (15 cm, residence time t^{R1} = 1.4 s) and introduced to **M1** (ϕ = 500 μm), where a solution of **2** (0.2 M in CH_2Cl_2) was also introduced (flow rate = 1.5 mL/min). The mixed solution was passed through **R2** (residence time t^{R2} s, T °C) and introduced to **M2** (ϕ = 500 μm), where Et_3N was also introduced (flow rate = 1.5 mL/min). The quenched reaction mixture was passed through **R3** (50 cm) and collected to a vessel for 60 s. After concentration under reduced pressure, the crude solution was passed through silica plug using Et_2O as an eluent to remove supporting electrolyte. After removing the solvent under reduced pressure, the crude mixture was analyzed by ^{1}H NMR using TCE as an internal standard. The results are summarized in Table S5.

Table S5. Kinetic Analysis of the *O*→*C*-Glycoside Rearrangement.

entry	T	**R2**	t^{R2}	yield of **3**	yield of **4α**	yield of **4β**
-	[°C]	[cm]	[s]	[%]	[%]	[%]
1	0	3.5	0.25	2.4	13.7	48.9
2	0	12.5	0.91	5.1	20.6	66.6
3	0	50	3.6	10.0	19.4	71.6
4	0	100	7.3	12.4	18.6	70.4
5	0	400	29.0	30.2	12.1	49.3
6	20	3.5	0.25	2.9	20.5	57.3
7	20	12.5	0.91	6.9	19.4	60.3
8	20	50	3.6	23.7	14.4	51.5
9	20	100	7.3	37.7	10.2	38.3
10	20	400	29.0	87.4	0	0

Continuous Production of *C*-Arylglycoside 3.

An electrochemical flow reactor system consisting of a divided electrochemical flow reactor, a T-shaped micromixer (**M1**), three microtube reactors (**R1**, **R2** and **R3**), and three pre-cooling units (**P1** (L = 200 cm), **P2** (200 cm) and **P3** (100 cm)) was used. The electrochemical reactor was cooled at 0 °C by a Peltier cooling system and two pre-cooling units **P1** and **P2** were cooled in acetone baths at 0 °C. The flow microreactor system composed of **P3**, **R1**, **R2** and **M1** was cooled in acetone bath at 0 °C, and **R3** was warmed in water bath at 20 °C. The plunger pumps (Shimadzu, LC-20AD) were used for the operation. During the operation, the amount of solution was monitored by sampling the solution and adjusted by changing diameter and length of tube reactor connected to the cathodic chamber. A solution of TfOH (0.05 M in 0.1 M Bu_4NBF_4/CH_2Cl_2, flow rate = 5.0 mL/min) was introduced to the cathodic chamber through **P1**. A solution of **1** (0.03 M in 0.1 M Bu_4NBF_4/CH_2Cl_2, flow rate = 5.0 mL/min) was introduced to the anodic chamber through **P2**. The constant current electrolysis was carried out at 0 °C. Current value was set to consume 1.25 F/mol of electricity (300 mA). The resulting solution from anodic chamber was passed through **R1** (15 cm, residence time t^{R1} = 1.4 s) and introduced to **M1** (ϕ = 500 μm), where a solution of **2** (0.2 M in CH_2Cl_2, flow rate = 2.3 mL/min) was also introduced. The mixed solution was passed through **R2** (50 cm, residence time t^{R2} = 3 s, 0 °C) and **R3** (1000 cm, residence time t^{R3} = 65 s, 20 °C). After a steady state was reached, aliquots of the reaction mixture were collected to a vessel containing Et_3N (20 mL) for 10 min. Continuous operation was carried out for 60 min, and the vessels were changed every 10 min. After concentration under reduced pressure, the crude solution was passed through

silica plug using Et_2O as an eluent. After concentration under reduced pressure, the crude mixture was analyzed by ^1H NMR using TCE as an internal standard. Then, the combined residue was purified by flash chromatography (hexane/ethyl acetate = 5/1 to 3/1) to obtain **3** (2.51g, 6.9 mmol, 77% yield).

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Chapter 4

Flash Cationic Polymerization of Vinyl Ethers Initiated by Dendritic Carbocations Using Flow Microreactors

Abstract

Flash cationic polymerization of vinyl ethers initiated by an electrooxidatively generated dendritic diarylcarbenium ion was achieved by using flow microreactors. Fast mixing of the highly reactive carbocation and vinyl ether in a micromixer enabled quick initiation of the polymerization and precise control of the molecular weight distribution. By controlling the residence time and the reaction temperature, unstable cationic polymer end was efficiently utilized for the trapping reaction with various nucleophiles and block copolymerization to give structurally well-defined linear-dendritic polymers.

Introduction

Linear-dendritic polymers have emerged as a new class of macromolecules in materials science,[1] and their characteristic structure offer unique/new possibilities for numerous potential applications.[2] In general, they can be synthesized by three strategies (Figure 1): (A) coupling strategy[3]: coupling of a dendritic unit and a functional linear polymer chain, (B) chain-first strategy[4]: the synthesis of a polymer chain bearing functional groups at the terminal and the subsequent construction of a dendrimer, and (C) dendron-first strategy[5]: the synthesis of a dendrimer from the core followed by polymerization initiated at the dendrimer. Especially the dendron-first approach is mainly employed because the dendrimers can be constructed by an established convergent synthetic route such as coupling of prefabricated branched units.

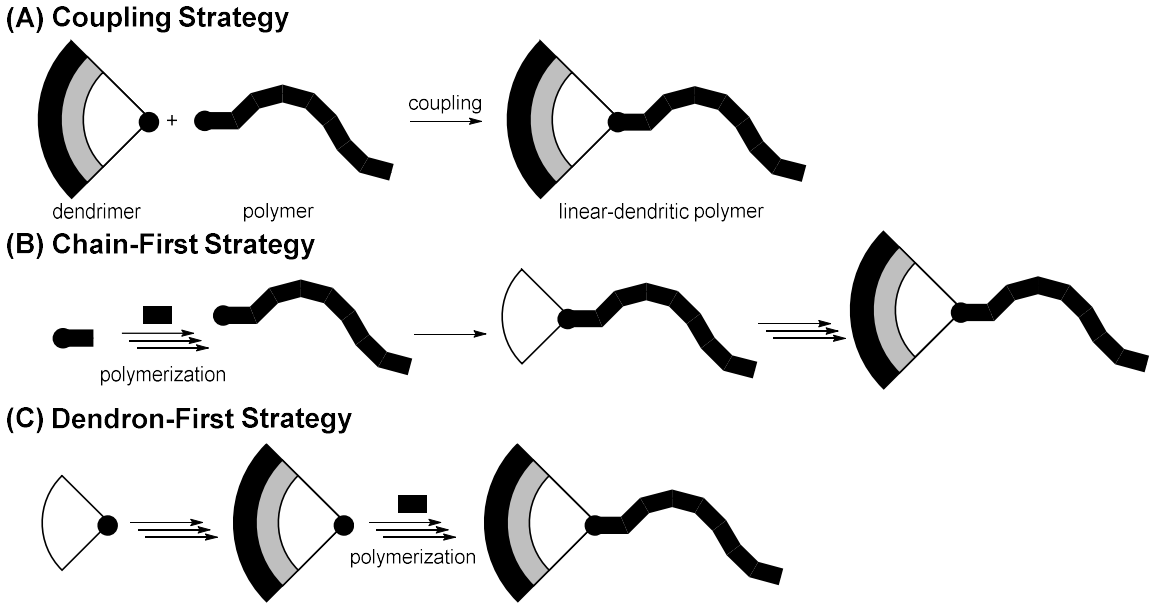


Figure 1. Synthetic strategies for linear-dendritic polymers; (A) coupling strategy, (B) chain-first strategy and (C) dendron-first strategy.

Recently, Yoshida and co-workers have developed the cation pool method, whereby highly reactive organic cations are generated by electrochemical oxidation and accumulated in solution in the absence of nucleophiles and are then used in subsequent reactions with various nucleophiles.[6] This methodology has been successfully applied to a variety of carbocations such as *N*-acyliminium ions, alkoxycarbenium ions, and diarylcarbenium ions. An iterative process for constructing dendritic structures based on this methodology have

also been developed; a sequence consisting of the electrochemical generation of a diarylcarbenium ion followed by the reaction with (diphenylmethyl)trimethylsilane as a building block is repeated for efficient convergent synthesis of dendritic molecules.[7] Notably, dendritic diarylcarbenium ions show high reactivity and react with the aromatic rings of polystyrenes to achieve direct dendronization of unfunctionalized polystyrene.[8]

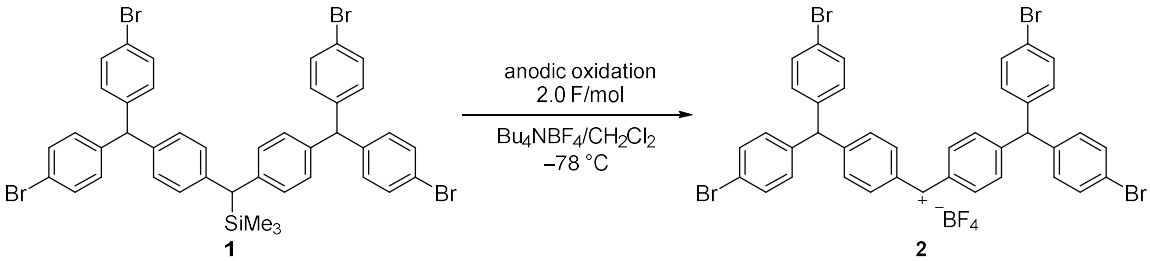
Flow microreactors[9-11] has attracted a great deal of attention and the applications to polymerization of vinyl monomers have been extensively studied.[12] For example, cationic polymerization of vinyl ethers[13] and anionic polymerization of styrenes, alkyl methacrylates, and *tert*-butyl acrylate using flow microreactors have been reported.[14] The molecular weight and the molecular weight distribution can be precisely controlled by virtue of the features of flow microreactors such as fast mixing, fast heat transfer, and precise residence time control.

Based on these backgrounds, the combination of electrooxidatively generated dendritic diarylcarbenium ions and flow microreactors would provide novel approach to linear-dendritic polymers. This chapter describes the development of flash cationic polymerization of vinyl ethers initiated by dendritic diarylcarbenium ion in flow microreactors. This method serves as a powerful and straightforward way of synthesizing structurally well-defined linear-dendritic polymers.

Results and Discussion

To test the feasibility of the present concept, diarylcarbenium ion **2**[8b] was chosen as a model dendritic initiator for the cationic polymerization. The carbocation **2** was generated by low-temperature electrochemical oxidation of **1**, which has a trimethylsilyl group as an electroauxiliary[15] for the selective oxidation and peripheral bromo functionalities for further functionalization (Scheme 1).

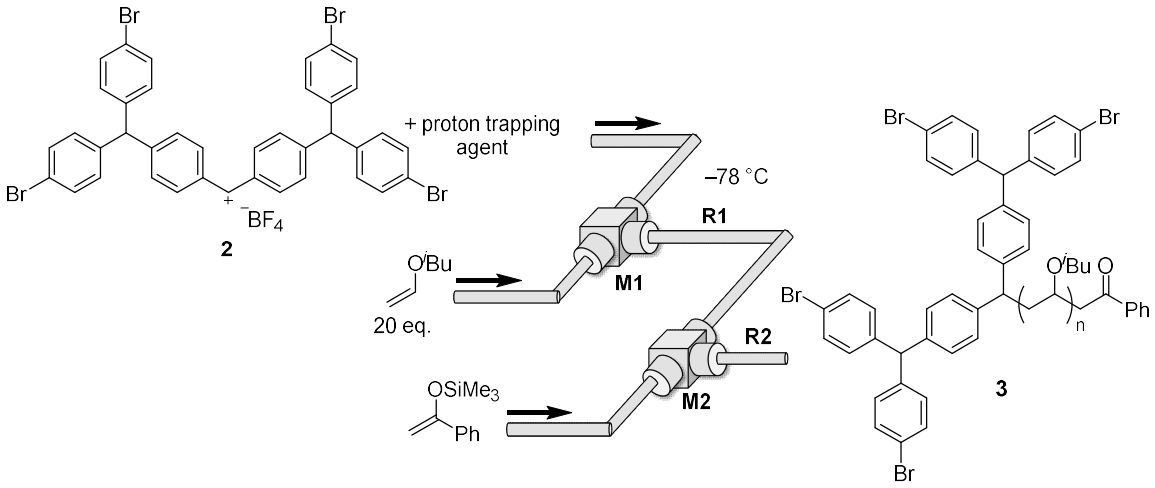
Scheme 1. Electrochemical Generation and Accumulation of Diarylcarbenium Ion **2**.



Cationic polymerization of isobutyl vinyl ether using **2** in a flow microreactor system

composed of two T-shaped micromixers (**M1** and **M2**) and two microtube reactors (**R1** and **R2**) was examined (Scheme 2). The flow microreactor system was dipped in a cooling bath (−78 °C). A solution of isobutyl vinyl ether (0.50 M in CH_2Cl_2, 10 mL/min) and a solution of **2** (0.050 M in CH_2Cl_2, 5 mL/min) were mixed in **M1** (ϕ = 250 μm), and the mixed solution passed through microtube reactor **R1** (ϕ = 1000 μm, L = 25 cm), where the polymerization took place. The polymerization was terminated by adding a solution of trimethyl(1-phenylvinyloxy)silane (1.0 M in CH_2Cl_2, 5 mL/min) at **M2** (ϕ = 500 μm) and **R2** (ϕ = 1000 μm, L = 50 cm) to obtain the polymer **3**.

Scheme 2. Flash Cationic Polymerization of Isobutyl Vinyl Ether Initiated by **2** in a Flow Microreactor System.



Obtained polymer was analyzed by MALDI-TOFMS, and the spectrum indicated that the polymer produced without additives was contaminated with a significant amount of the proton-initiated one (Figure 2a). To suppress such polymers, screening of a proton trapping agent was conducted (Table 1). For the screening, proton trapping agents were added to a solution of **2** prior to the polymerization. Although **3** was obtained in good yields in the absence of a proton trapping agent (Table 1, entry 1), polymerizations in the presence of 1,8-bis(dimethylamino) naphthalene resulted in much low yield presumably due to the reaction of the trapping agent and cation **2** (Table 1, entries 2-4). In contrast, the use of 2,6-di-*tert*-butylpyridine as a proton trapping agent resulted in a dramatic decrease in the amount of the polymer formed by the proton initiation without a decreasing in yield (Figure 2b and Table 1, entries 5-7). The results indicate that protons generated during the anodic oxidation were effectively removed by 2,6-di-*tert*-butylpyridine. Therefore, the desired polymer **3** with narrow molecular weight distribution (M_w/ M_n = 1.05) was obtained, indicating that diarylcarbenium ion **2** worked well as an initiator.

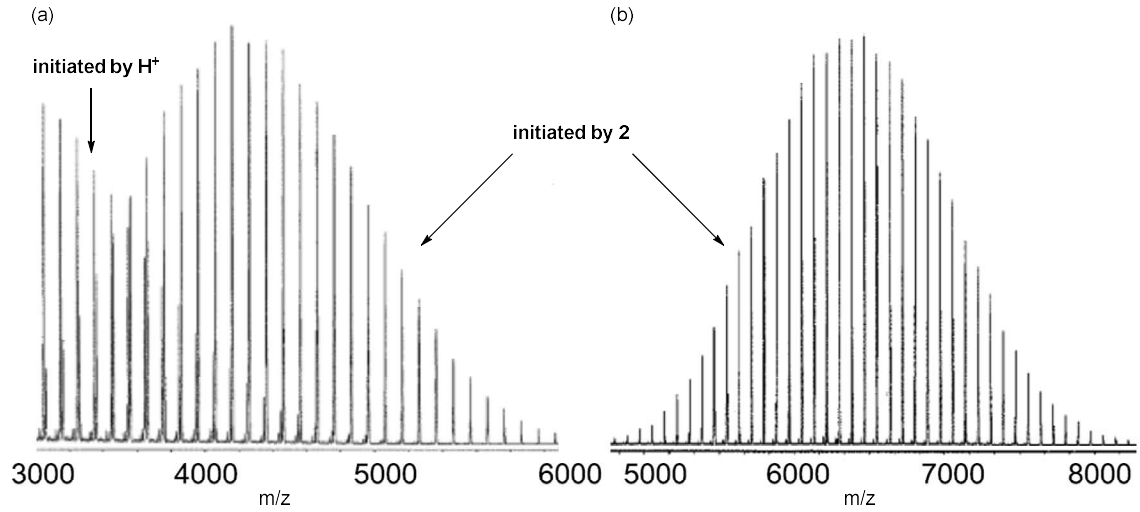
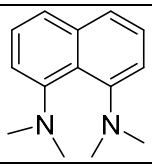
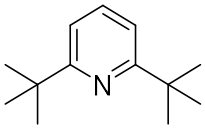


Figure 2. MALDI-TOFMS spectra of the polymers obtained by (a) the polymerization without a proton trapping agent and (b) the polymerization with 0.5 equivalent of 2,6-di-*tert*-butylpyridine.

Table 1. Effect of Proton Trapping Agents for Cationic Polymerization.

entry	proton trapping agent		M_n[a]	M_w/M_n[a]	yield [%]
1	-	-	5,200	1.08	quant.
2		0.3 eq.	13,400	1.10	61
3		0.5 eq.	12,100	1.19	22
4		1.0 eq.	16,100	1.11	6
5		0.3 eq.	6,600	1.06	87
6		0.5 eq.	8,100	1.05	83
7		1.0 eq.	9,000	1.05	90

[a] Polymers were analyzed with size exclusion chromatography calibrated with polystyrene.

Next, the effect of mixing was examined. First, the polymerization in the presence of 2,6-di-*tert*-butylpyridine (0.5 eq.) using a batch macro reactor was performed. The addition of **2** (0.050 M in CH_2Cl_2) with 2,6-di-*tert*-butylpyridine (5 mL, 5.0 mL/min) to a solution of isobutyl vinyl ether (10 mL, 0.50 M in CH_2Cl_2) in a flask (25 mL) gave the polymer in 84% yield after quenching with trimethyl(1-phenylvinyloxy)silane (1.0 mL, 1.0 M in CH_2Cl_2), but the molecular weight distribution was relatively broad (M_n = 26,600, M_w/M_n = 1.45). The reverse addition gave rise to only a slight improvement of the similar molecular weight distribution control (97% yield, M_n = 7,600, M_w/M_n = 1.29). The simultaneous addition gave disappointing result (96% yield, M_n = 11,200, M_w/M_n = 1.59). Thus, it is reasonable to

consider that fast mixing, which is the characteristic feature of a flow microreactor system is effective to control the initiation reaction. Second, details on the effect of micromixer were investigated. In general, the time required to complete the mixing is known to depend on the flow rate and the inner diameter of a micromixer.[16] As shown in Table 2, the molecular weight distribution (M_w/M_n) strongly depends on the flow rate and the inner diameter of micromixer **M1**. The molecular weight distribution decreased with the increase in the flow rate of solutions in **M1** (Table 2, entries 1-3). The M_w/M_n also decreased when the inner diameter of **M1** was reduced. These results indicate that extremely fast mixing in micromixers is responsible for narrow molecular weight distribution.

Table 2. Effect of Fast Mixing for Cationic Polymerization of Isobutyl Vinyl Ether.

entry	inner diameter of **M1** [mm]	total flow rate in **M1** [mL/min]	M_n[a]	M_w/M_n[a]	yield [%]
1	250	3.0	8,600	2.03	55
2	250	9.0	7,000	1.11	99
3	250	15.0	8,100	1.05	83
4	500	15.0	6,100	1.16	95

[a] Polymers were analyzed with size exclusion chromatography calibrated with polystyrene.

In addition to trimethyl(1-phenylvinyloxy)silane, allyltrimethylsilane served as a good terminating agent to obtain the desired end-functionalized polymer **4** with narrow molecular weight distribution (83% yield, M_n = 7,500, M_w/M_n = 1.06). The ^{1}H NMR spectra of **3** and **4** showed that the two methine protons (H^a) derived from **2** was clearly observed at δ = 5.37 ppm (Figure 3). The end group such as an aryl group (for **3**: aromatic protons, δ = 7.45, 7.55 and 7.96 ppm) and as an allyl group (for **4**: olefinic protons, δ = 5.01-5.06 and 5.78-5.84 ppm) were also observed. The relative intensities of these protons based on the methine proton (H^a) indicated that the cationic polymer end was effectively trapped by carbon nucleophiles. These results showed that the present method was effective for construction of linear-dendritic polymers in a highly controlled manner.

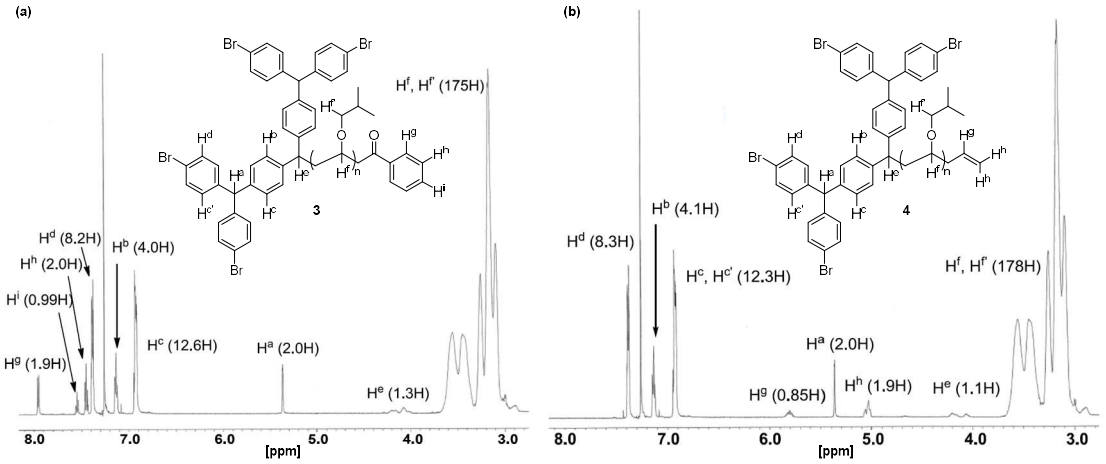
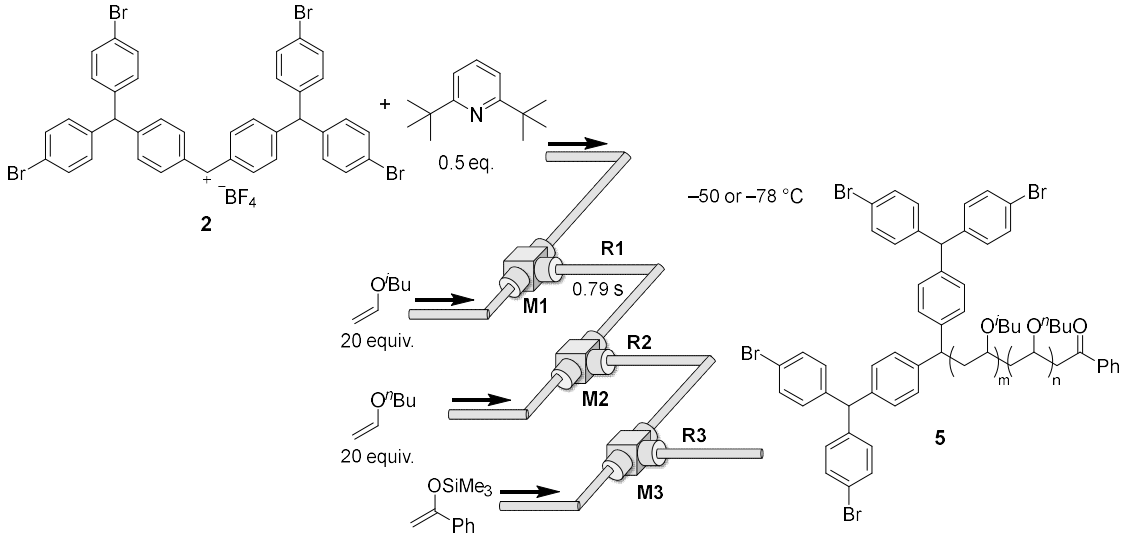


Figure 3. ^{1}H NMR spectra of end-functionalized linear-dendritic polymers; (a) **3** and (b) **4**.

Finally, the block copolymerization of isobutyl vinyl ether and *n*-butyl vinyl ether was performed (Scheme 3). After the homopolymerization of isobutyl vinyl ether initiated by **2** in **M1** and **R1**, the solution of *n*-butyl vinyl ether (1.0 M in CH_2Cl_2, 5 mL/min) was introduced to **M2** (ϕ = 500 μm) and the second polymerization of *n*-butyl vinyl ether proceeded in **R2** (ϕ = 1000 μm, L = 50 cm (–50 °C) or ϕ = 1000 μm, L = 100 cm (–78 °C)). The polymerization was terminated by introducing a solution of trimethyl(1-phenylvinyloxy)silane (1.0 M in CH_2Cl_2, 5 mL/min) to **M3** (ϕ = 500 μm) and **R3** (ϕ = 1000 μm, L = 50 cm).

Scheme 3. Integrated Flow Microreactor System for Cationic Block Copolymerization of Isobutyl Vinyl Ether and *n*-Butyl Vinyl Ether.



GPC traces of the polymers **5** obtained at various temperature are shown in Figure 4. The increasing in M_n was observed when the second monomer solution was added at −50 °C, indicating that the polymerization of the second monomer took place. However, the bimodal molecular weight distribution indicated decomposition of the cationic polymer end generated by the first polymerization (Figure 4a). On the other hand, the block copolymerization was successfully achieved without significant decomposition of the living polymer end at −78 °C with a short residence time in **R1** (0.79 s) to obtain **5** in 95% yield with narrow molecular weight distribution (M_w/M_n = 1.08) as shown in Figure 4b.

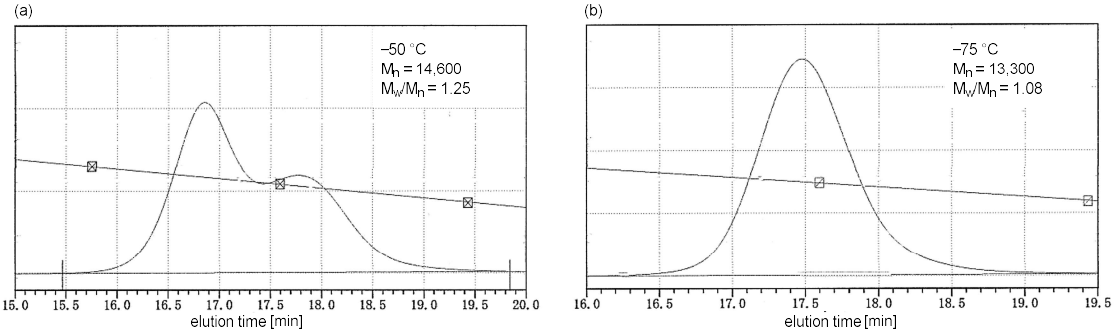


Figure 4. Size exclusion chromatography traces of the cationic block copolymerization of isobutyl vinyl ether and n-butyl vinyl ether (a) at −50 °C and (b) at −75 °C with the residence time of 0.79 s in **R1**.

The ^{1}H NMR analyses of **5** revealed that the end functional group was introduced almost quantitatively (Figure 5). Notably, the block copolymer **5** bearing bromo groups at the peripheral of the dendritic part can be used for further transformations such as Hartwig-Buchwald amination.[17]

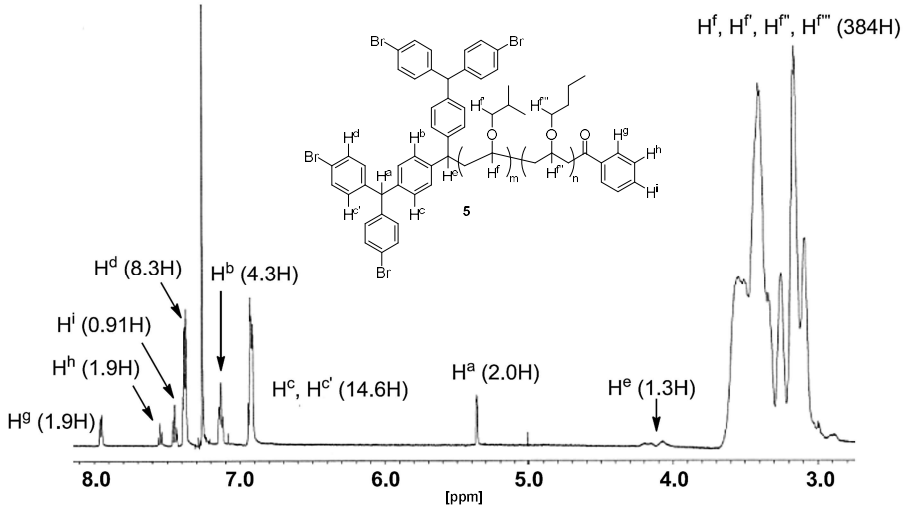


Figure 5. ^{1}H NMR of block copolymer **5**.

Conclusion

In conclusion, controlled flash cationic polymerization of vinyl ethers initiated by a dendritic diarylcarbenium ion was successfully achieved using a flow microreactor system. Fast mixing in micromixer is responsible for narrow molecular weight distribution. The transient cationic polymer end can be utilized for the subsequent reactions with nucleophiles and block copolymerization by precise temperature and residence time control. The results described here will open a new possibility in the synthesis of linear-dendritic polymers.

Experimental section

General.

^{1}H NMR spectra were recorded in $CDCl_3$ on JEOL ECA-600P (^{1}H: 600 MHz and ^{13}C: 150 MHz). Chemical shifts are recorded using a methine signal of $CDCl_3$ for ^{1}H NMR (7.26 ppm) unless otherwise noted. MALDI-TOFMS spectra were recorded on Bruker ultraflex. Preparative gel permeation chromatography (GPC) was performed on Japan Analytical Industry LC-918. The molecular weight (M_n) and molecular weight distribution (M_w/M_n) were determined in THF at 40 °C with a Shodex GPC-101 equipped with two LF-804L columns (Shodex) and an RI detector using polystyrene standard samples for calibration. Stainless steel (SUS304) T-shaped micromixers with inner diameter of 250 and 500 μm were manufactured by Sanko Seiki Co., Inc. Stainless steel (SUS316) microtube reactors with inner diameter of 1000 μm were purchased from GL Sciences. The micromixers and microtube reactors were connected with stainless steel fittings (GL Sciences, 1/16 OUW). The solutions were introduced to the flow microreactor system using Harvard Model 11 syringe pumps equipped with gastight syringes purchased from SGE. All solutions used for reactions were prepared under the argon atmosphere using dry solvents. Dichloromethane was washed with water, distilled from P_2O_5, redistilled from dried K_2CO_3 to remove a trace amount of acid, and stored over molecular sieves 4A. Isobutyl vinyl ether and *n*-butyl vinyl ether were distilled under reduced pressure from CaH_2 twice. Bu_4NBF_4 was dried at 25 °C/1 mmHg for 12 h. **1** was prepared according to reported procedure.[8b] Unless otherwise noted, all materials were purchased from commercial suppliers and were used without further purification.

Electrochemical Generation and Accumulation of Diarylcarbenium Ion 2.

The anodic oxidation was carried out in an H-type divided cell (4G glass filter) equipped

with a carbon felt anode (Nippon Carbon JF-20-P7, ca. 320 mg, dried at 250 °C/1 mmHg for 2.5 h before use) and a platinum plate cathode (20 mm × 10 mm). A solution of **1** (1.55 g, 1.75 mmol) in 0.3 M Bu_4NBF_4/CH_2Cl_2 (35 mL) was placed in the anodic chamber, and a 0.3 M solution of Bu_4NBF_4/CH_2Cl_2 (35 mL) and trifluoromethanesulfonic acid (230 μL, 2.60 mmol) were placed in the cathodic chamber. The constant current electrolysis (40 mA) was carried out at −78 °C with magnetic stirring until 2.0 F/mol of electricity was consumed (ca. 140 min). After electrolysis, the solution of **2** was transferred by dried glass syringe at −78 °C for next polymerization.

General Procedure for Cationic Polymerization of Isobutyl Vinyl Ether Using a Flow Microreactor System.

After the anodic oxidation of **1**, the solution of **2** was transferred to a 20 mL flask at −78 °C. Then 2,6-di-*tert*-butylpyridine was added and the resulting solution was stirred for 10 min at −78 °C. 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** (inner diameter ϕ = 1000 μm, length L = 25 cm), **P2** (ϕ = 1000 mm, L = 50 cm) and **P3** (ϕ = 1000 mm, L = 50 cm)) was used. A solution of isobutyl vinyl ether (0.50 M in CH_2Cl_2, 10 mL/min) and a solution of **2** containing the proton trapping agent (0.05 M, 5 mL/min) were introduced to **M1** (ϕ = 250 μm). The mixed solution was passed through **R1** (ϕ = 1000 mm, L = 25 cm) and was introduced to **M2** (ϕ = 500 μm). A solution of trimethyl(1-phenylvinyloxy)silane (1.0 M in CH_2Cl_2, 5 mL/min) was introduced to **M2** (ϕ = 500 μm), and the resulting solution was passed through **R2** (ϕ = 1000 μm, L = 50 cm). After a steady state was reached, the reaction solution was collected (10 s) and treated with $^{i}Pr_2NH$. The solvent was removed under reduced pressure and the residue was filtered through a silica gel column using Et_2O as an eluent to remove Bu_4NBF_4. The filtrate was concentrated to obtain a crude polymer product, which was analyzed with size exclusion chromatography and purified by preparative GPC to give **3**.

Cationic Polymerization of Isobutyl Vinyl Ether Using a Macro Batch Reactor.

The cationic polymerization of isobutyl vinyl ether with **2** was carried out in a glass flask (20 mL) at −78 °C. For comparison, the following three methods were examined.

Method A.

A solution of **2** (0.05 M in CH_2Cl_2) and 2,6-di-*tert*-butylpyridine (0.5 eq. based on **1**) were mixed, and the mixture was added to a solution of isobutyl vinyl ether (10 mL, 0.50 M in CH_2Cl_2) at −78 °C using a syringe pump (flow rate = 5.0 mL/min). The reaction mixture was stirred for 1 min at the same temperature and a solution of

trimethyl(1-phenylvinyloxy)silane (1.0 mL, 1.0 M in CH_2Cl_2) was added. After stirring for 1 min at the same temperature, $^{i}Pr_2NH$ (2.0 mL) was added. Then the crude product was treated according to the protocol described above to obtain a product (84% yield), which was analyzed with size exclusion chromatography (M_n = 26,600, M_w/M_n = 1.45).

Method B.

A solution of isobutyl vinyl ether (10 mL, 0.50 M in CH_2Cl_2) was added to a mixture solution of **2** (0.05 M in CH_2Cl_2) and 2,6-di-*tert*-butylpyridine (0.5 eq. based on **1**, 5 mL) at −78 °C using a syringe pump (flow rate = 10 mL/min). The reaction mixture was stirred for 1 min at the same temperature and a solution of trimethyl(1-phenylvinyloxy)silane (1.0 mL, 1.0 M in CH_2Cl_2) was added. After stirring for 1 min at the same temperature, $^{i}Pr_2NH$ (2.0 mL) was added. Then the crude product was treated according to the protocol described above to obtain a product (97% yield), which was analyzed with size exclusion chromatography (M_n = 7,560, M_w/M_n = 1.29).

Method C.

A solution of isobutyl vinyl ether (10 mL, 0.50 M in CH_2Cl_2) and a mixture of **2** (0.05 M in CH_2Cl_2) 2,6-di-*tert*-butylpyridine (0.5 eq. based on **1**, 5 mL) were simultaneously added to a glass flask at −78 °C by using syringe pumps (flow rate = 10 mL/min for isobutyl vinyl ether, 5.0 mL/min for **2**). The reaction mixture was stirred for 1 min at the same temperature and a solution of trimethyl(1-phenylvinyloxy)silane (1.0 mL, 1.0 M in CH_2Cl_2) was added. After stirring for 1 min at the same temperature, $^{i}Pr_2NH$ (2.0 mL) was added. Then the crude product was treated according to the protocol described above to obtain a product (96% yield), which was analyzed with size exclusion chromatography (M_n = 11,200, M_w/M_n = 1.59).

General Procedure for Block Copolymerization of Isobutyl Vinyl Ether and *n*-Butyl Vinyl Ether Using an Integrated Flow Microreactor System.

After the anodic oxidation of **1**, a solution of **2** (6 mL, −78 °C) was transferred to a 20 mL flask at −78 °C and 2,6-di-*tert*-butylpyridine (0.5 eq. based on **1**) was added at the same temperature. The resulting solution was stirred for 10 min at −78 °C. An integrated 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** (inner diameter ϕ = 1000 μm, length L = 25 cm), **P2** (ϕ = 1000 μm, L = 50 cm), **P3** (ϕ = 1000 μm, L = 50 cm), and **P4** (ϕ = 1000 μm, L = 50 cm)) was used. A solution of isobutyl vinyl ether (0.50 M in CH_2Cl_2, 10 mL/min) and a solution of **2** containing 2,6-di-*tert*-butylpyridine (5 mL/min) were introduced to **M1** (ϕ = 250 μm). The mixed solution was passed through **R1** (ϕ = 1000

mm, L = 25 cm) and was introduced to **M2** (ϕ = 500 μm). A solution of *n*-butyl vinyl ether (1.0 M in CH_2Cl_2, 5 mL/min) was introduced to **M2** (ϕ = 500 μm). The mixed solution was passed through **R2** (ϕ = 1000 μm, L = 100 cm) and was introduced to **M3** (ϕ = 500 μm). A solution of trimethyl(1-phenylvinyloxy)silane (1.0 M in CH_2Cl_2, 5 mL/min) was introduced to **M3** (ϕ = 500 μm), and the resulting solution was passed through **R3** (ϕ = 1000 μm, L = 50 cm). After a steady state was reached, the product solution was collected (10 s) and treated with $^{i}Pr_2NH$. Then the crude product was treated according to the protocol described above to obtain a product (95% yield), which was analyzed with size exclusion chromatography (M_n = 13,300, M_w/M_n = 1.08). The crude product was purified by preparative GPC to obtain **5**.

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Chapter 5

A Novel Approach to Linear-Dendritic Hybrid Polymers Based on Flash Cationic Polymerization and Bis-end-functionalization

Abstract

A novel synthetic approach to linear-dendritic hybrid polymer was developed using cationic polymerization followed by transition metal-catalyzed transformations. Flash cationic polymerization of vinyl ethers using a multifunctional dendritic initiator and multifunctional terminators in a flow microreactor system was achieved within seconds to give polymers with multiple functionalities on both polymer ends. Subsequent transformation through palladium-catalyzed cross-coupling and/or copper-mediated azide-alkyne cycloaddition gave structurally well-defined linear-dendritic hybrid polymers.

Introduction

Macromolecules with complex structure are drawing increasing attention in the search for novel materials with unconventional and/or improved properties. Linear-dendritic (L-D) polymers[1] are intriguing and promising macromolecules in materials science, and their characteristic structure offer unique possibilities for numerous emerging applications.[2] In general, three strategies are employed for synthesizing L-D polymers (Figure 1): (a) dendron-first strategy[3]: the synthesis of a dendrimer followed by polymerization initiated at the dendrimer, (b) coupling strategy[4]: coupling of a dendrimer and a functional linear polymer chain, and (c) chain-first strategy[5]: the synthesis of a terminally functionalized polymer chain and the subsequent construction of a dendrimer.

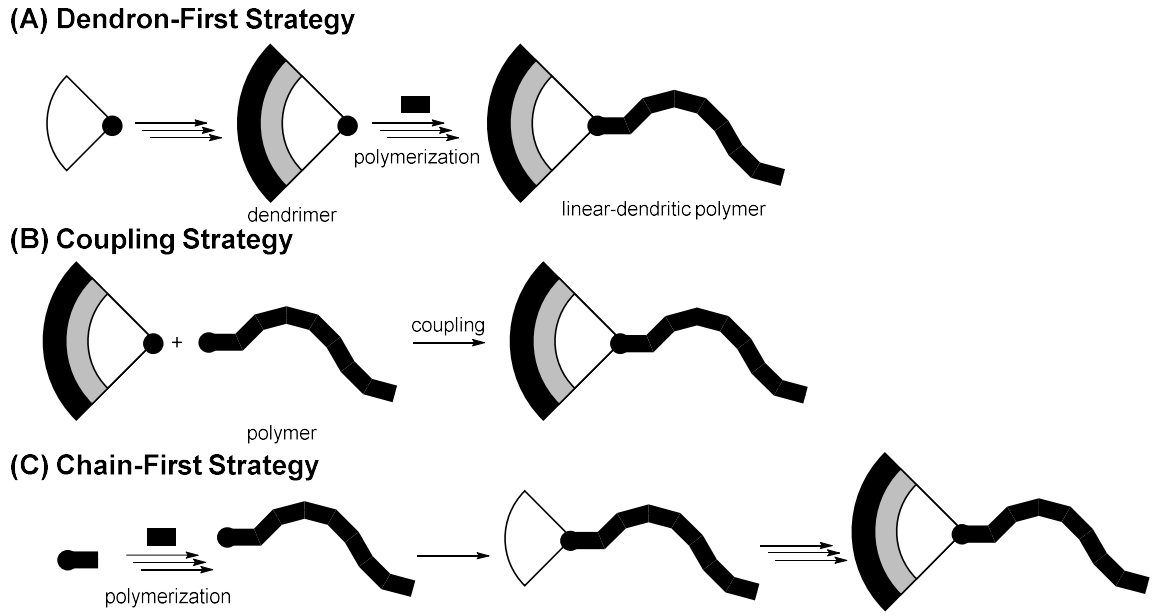
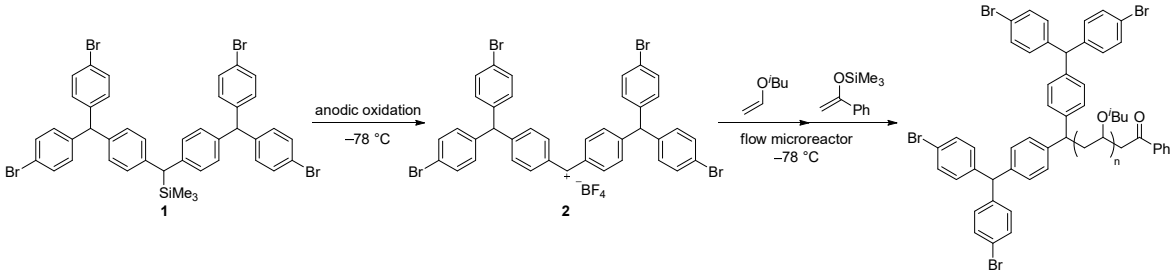


Figure 1. Synthetic strategies for linear-dendritic polymers; (a) dendron-first strategy, (b) coupling strategy and (c) chain-first strategy.

In chapter 4, a dendron-first approach to linear-dendritic polymers through cationic polymerizations of vinyl ethers initiated by anodically generated dendritic diarylcarbenium ion **2** using a flow microreactor was described (Scheme 1).[6] The fast polymerization could be precisely controlled by the features of flow microreactors,[7–9]fast mixing, fast heat transfer and precise residence time control, achieving living polymerization[10,11] and narrow molecular weight distribution. Notably, the living polymer end could be used for block-copolymerization and trapping reaction with various carbon nucleophiles. In addition,

the reaction tolerates useful bromide moieties derived from **2**. Based on these developments, it is envisaged that by employing a properly functionalized terminator in the method, polymers with functionalities on both ends would be obtained. Subsequent transformation of the resulting multifunctional polymers provides a new synthetic route to L-D polymers.

Scheme 1. Flash Synthesis of Linear-dendritic Polymers Using Flow Microreactors.



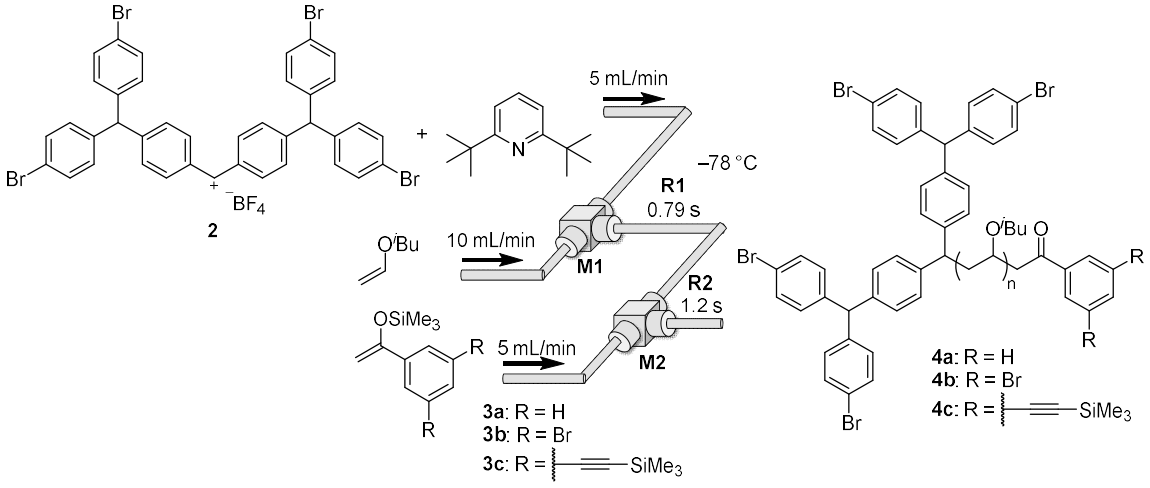
In this chapter, a proof-of principle study of synthesizing a series of novel L-D and D-L-D type polymers is described. At first step, end-functionalized polymers are synthesized by flash cationic polymerization using dendritic initiator **2** (dendron-first strategy). Then subsequent transition-metal-catalyzed transformations such as Suzuki-Miyaura cross-coupling[12] and Cu-mediated azide-alkyne cycloaddition (Cu-AAC)[13] afford well-defined D-L-D type polymers.

Results and Discussion

Initially, three functionalized polymers **4a**–**4c** were prepared by the cationic polymerization of isobutyl vinyl ether initiated by **2** and terminated by silyl enol ethers **3a**–**3c** in a flow microreactor system (Scheme 2). A solution of isobutyl vinyl ether (0.50 M in CH_2Cl_2, 10 mL/min) and a solution of **2** (prepared from 0.050 M of **1** in CH_2Cl_2, 5 mL/min) were mixed at T-shaped micromixer **M1** (ϕ = 250 μm) to initiate the polymerization. Note that adding 2,6-di-*tert*-butylpyridine (0.5 eq. to **1**) to the solution of **2** prior to the flow reaction was effective for removing electrogenerated acid. The mixed solution was passed through **R1** (ϕ = 1000 μm, L = 25 cm), where the polymerization proceeded. The polymerization was terminated by adding a solution of **3a** (1.0 M in CH_2Cl_2, 5 mL/min) at **M2** (ϕ = 500 μm) and **R2** (ϕ = 1000 μm, L = 50 cm). The whole flow system was dipped in a cooling bath and the reaction temperature was controlled at −78 °C. The desired polymer **4a** was obtained with good yield and narrow molecular weight distribution (91%, M_n = 8,600, M_w/M_n = 1.10). Extremely fast micromixing is responsible for narrow molecular weight distribution which cannot be attained in a conventional batch reactor.[6] Using **3b** and **3c** as terminating reagents, the same conditions also worked to afford

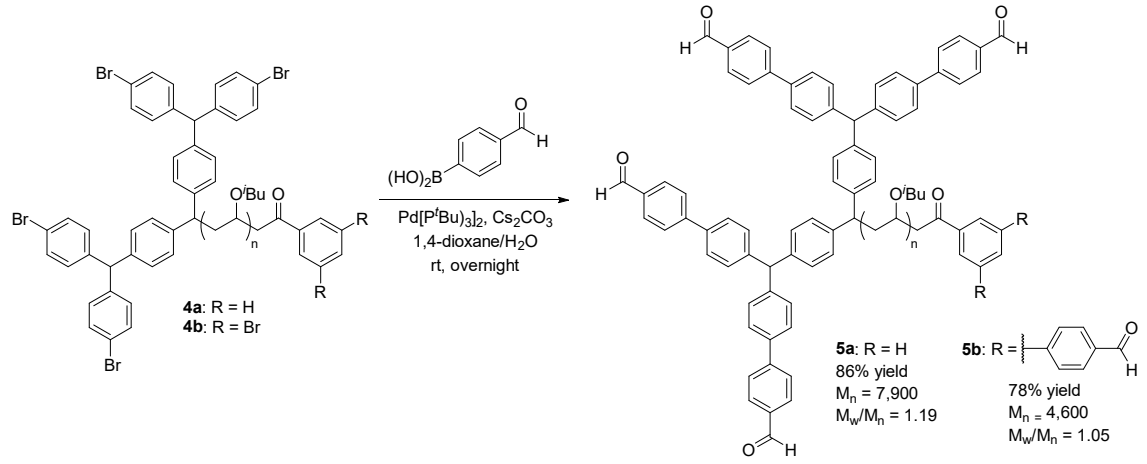
corresponding functionalized polymers **4b** and **4c**, respectively, showing the versatility of this method. Size exclusion chromatography (SEC) analysis showed that both polymers **4b** and **4c** had molecular weight distributions of 1.06 and 1.08, respectively (**4b**: M_n = 5,900, **4c**: M_n = 7,100).

Scheme 2. Flash Cationic Polymerization of Isobutyl Vinyl Ether Initiated by **2** and Terminating Reaction with **3** in a Flow Microreactor System.



Next, the transformation of aryl bromide moieties on the polymer ends of **4a** and **4b** were investigated through Suzuki-Miyaura cross-coupling reactions with an arylboronic acid (Scheme 3). 4-Formylphenylboronic acid was chosen as a coupling partner to monitor the progress of the reaction by ^{1}H NMR. By using Pd[P(^{t}Bu)$_3$]$_2$ and Cs_2CO_3, which are typical reagents for cross-coupling reactions, both **4a** and **4b** were smoothly reacted at room temperature. The corresponding L-D type polymer **5a** and D-L-D type polymer **5b** were obtained in 86% and 78% yield after purification with preparative gel permeation chromatography (GPC) (**5a**: M_n = 7,900, M_w/M_n = 1.19, **5b**: M_n = 4,600, M_w/M_n = 1.05). The ^{1}H NMR analyses indicated quantitative conversion to the corresponding coupling products because the shift of the specific peaks of the starting polymers were observed. As for the coupling reaction of **4a**, methine proton H^A derived from dendritic unit was shifted from δ = 5.36 ppm to δ = 5.59 ppm, and aldehyde protons H^B was newly appeared at δ = 10.05 ppm (Figure 2).

Scheme 3. Suzuki-Miyaura Cross-coupling Reactions of **4a**/**4b** with 4-Formylphenylboronic Acid.



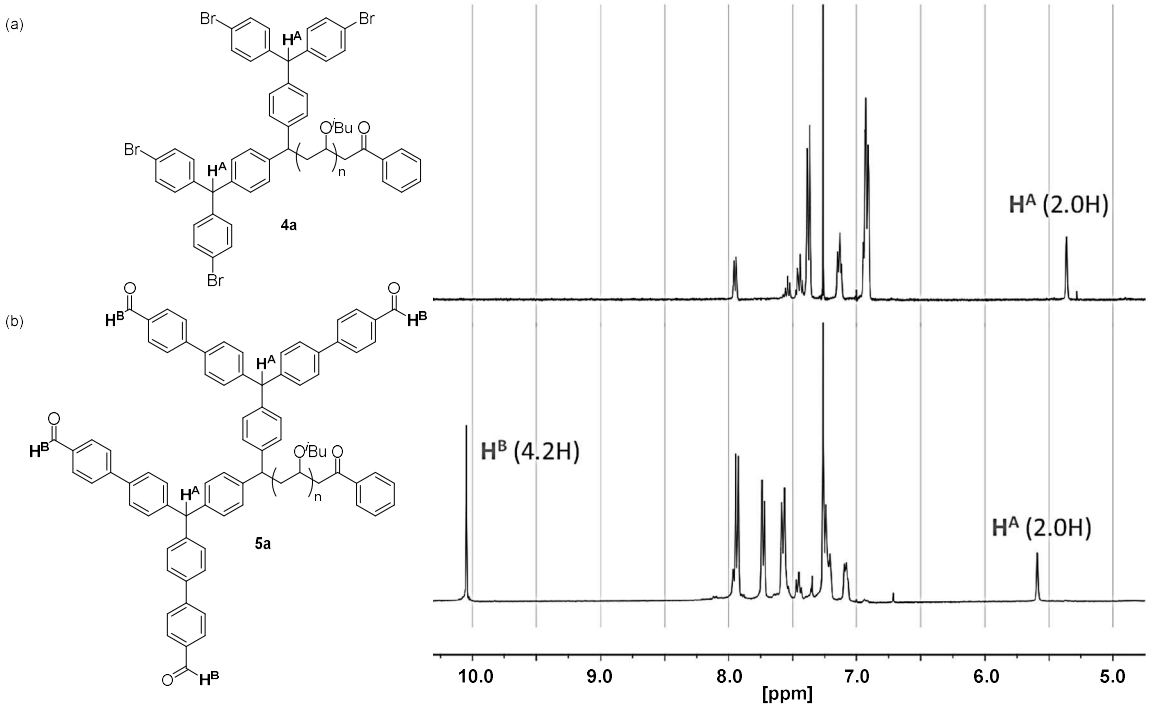


Figure 2. ^{1}H NMR spectra before (a; **4a**) and after (b; **5a**) Suzuki-Miyaura coupling reactions (400 MHz, in $CDCl_3$).

In the case of **4b**, a similar shift of methine proton H^A was observed (shifted from δ = 5.36 ppm to δ = 5.59 ppm), and two new peaks appeared at δ = 10.04 and 10.10 ppm, which could be assigned to aldehyde protons H^B and H^C (Figure 3). The relative intensities of the peaks assigned to H^A, H^B and H^C were; 2.0:4.2 for **5a**, 2.0:4.1:1.9 for **5b**. These ^{1}H NMR results strongly support the well-defined end structures of the L-D polymers.

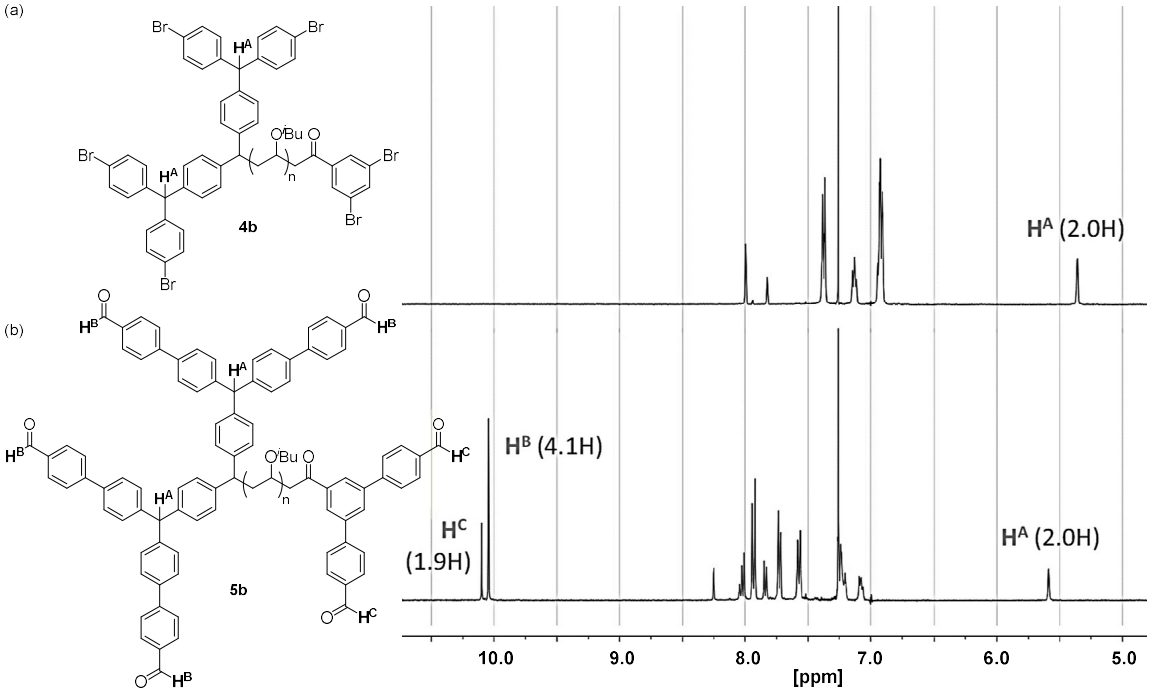
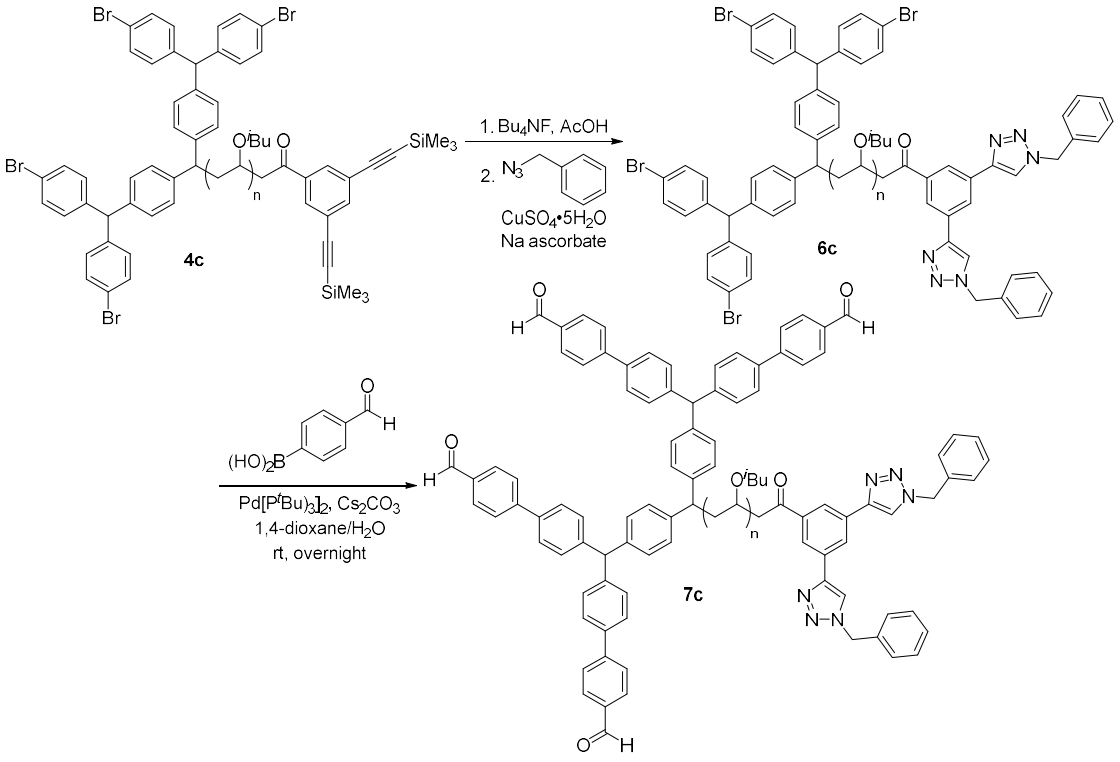


Figure 3. ^{1}H NMR spectra before (a; **4b**) and after (b; **5b**) Suzuki-Miyaura coupling reactions (400 MHz, in $CDCl_3$).

Finally, since polymer **4c** has two distinct functionalities of bromide and alkyne at each end, the sequential transformation of **4c** by utilizing Cu-AAC and Suzuki-Miyaura coupling was performed (Scheme 4). First, deprotection of trimethylsilyl group with tetrabutylammonium fluoride and acetic acid and the subsequent Cu-AAC reaction with benzyl azide in the presence of $CuSO_4 \cdot 5H_2O$ and sodium ascorbate using water as the co-solvent at 40 °C. After 2.5 h, the reaction was quenched and purified by GPC to give **6c** in 99% yield. ^{1}H NMR analysis showed downfield shift of aromatic protons H^B from δ = 7.94 ppm to δ = 8.30 ppm and appearance of a new peak at δ = 5.58 ppm that can be assigned to benzylic protons H^C, indicating quantitative conversion of the starting polymer **4c** to desired product **6c** (99%, M_n = 6,600, M_w/M_n = 1.07) (Figure 4a and 4b). Subsequent Suzuki-Miyaura coupling of aryl bromide moieties and arylboronic acid under the conditions similar to those for **4a** and **4b** afforded differently end-functionalized D^1-L-D^2 type polymer **7c** (M_n = 7,300, M_w/M_n = 1.07) in 85% yield. ^{1}H NMR analysis confirmed the quantitative conversion of the bromide groups on dendritic polymer ends, which was evident from a new peak at δ = 10.04 ppm that can be assigned to aldehyde protons H^D (Figure 4c).

Scheme 4. Sequential Transformations of **4c** with Cu-AAC and Suzuki-Miyaura Coupling.



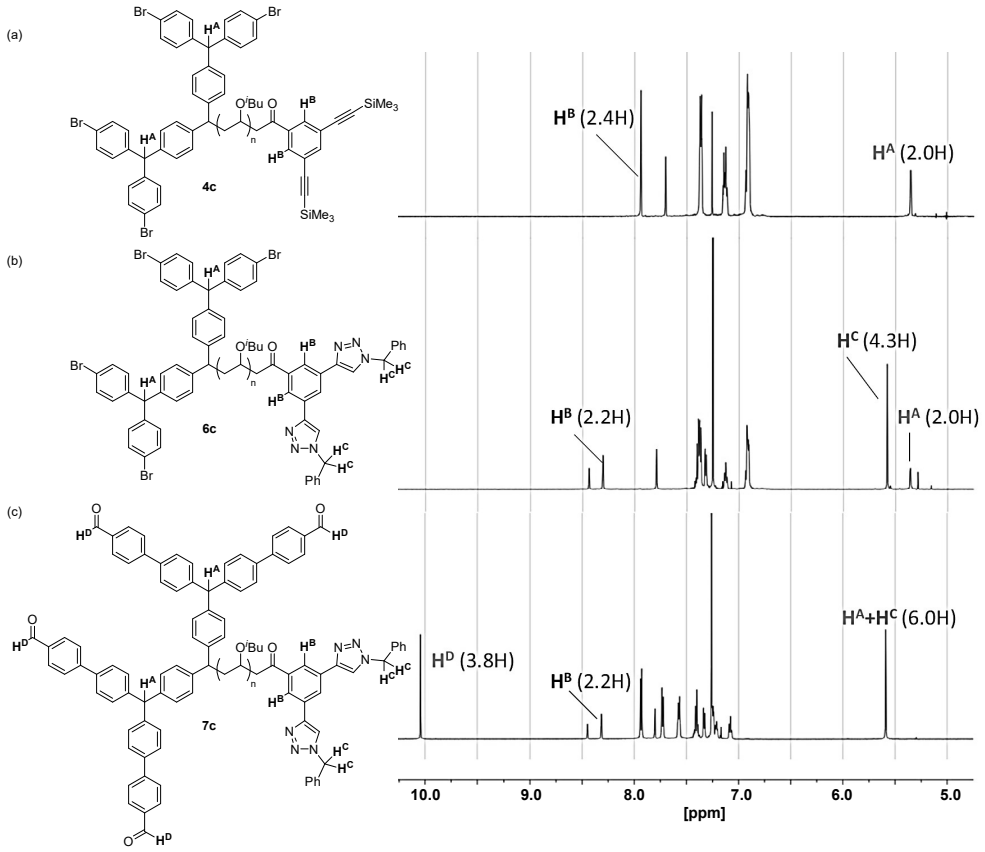


Figure 4. ^{1}H NMR spectra (a) before and (b) after Cu-AAC, and (c) after Suzuki-Miyaura coupling (600 MHz, in $CDCl_3$).

Conclusion

Rapid and precise synthesis of dendritic-linear-dendritic hybrid polymers was successfully achieved by utilizing a multifunctional dendritic diarylcarbenium ion and a multifunctional nucleophile based on flash cationic polymerization in a flow microreactor system and subsequent transition metal-catalyzed transformation of both polymer ends. The present proof-of-principle study opens a new synthetic route to linear-dendritic hybrid polymers including asymmetrically functionalized dendritic-linear-dendritic type polymers.

Experimental section

General.

^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Varian MERCURY plus-400 (^{1}H: 400 MHz, ^{13}C: 100 MHz) or a JEOL ECA-600P (^{1}H: 600 MHz and ^{13}C: 150 MHz). Chemical shifts are recorded using TMS (0.0 ppm) or $CDCl_3$ (7.26 ppm) signals as an internal standard for ^{1}H NMR, and methin signal of $CDCl_3$ for ^{13}C NMR (77.0 ppm) unless otherwise noted. Mass spectra were recorded on a JEOL JMS-700 (EI). The molecular weight (M_n) and molecular weight distribution (M_w/M_n) were determined in THF at 40 °C with a Shodex GPC-101 equipped with two LF-804L columns (Shodex) and an RI detector using polystyrene standard samples for calibration. TLC analyses were performed on commercial glass plates bearing a 0.25 mm layer of Merck Silica gel 60 F_{254}. Column chromatography was carried out on silica-gel (Kanto N60, spherical, neutral, 63–210 μm). Preparative gel permeation chromatography (GPC) was performed on Japan Analytical Industry LC-918. Stainless steel (SUS304) T-shaped micromixers with inner diameter of 250 and 500 μm were manufactured by Sanko Seiki Co., Inc. Stainless steel (SUS316) microtube reactors with inner diameter of 1000 μm were purchased from GL Sciences. The micromixers and microtube reactors were connected with stainless steel fittings (GL Sciences, 1/16 OUW). The solutions were introduced to the flow microreactor system using Harvard Model 11 syringe pumps equipped with gastight syringes purchased from SGE. All solutions used for reactions were prepared under the argon atmosphere using dry solvents. Isobutyl vinyl ether was distilled under reduced pressure from CaH_2 twice. Bu_4NBF_4 was dried at 25 °C/1 mmHg for 12 h. **1** was prepared according to reported procedure.[14] Unless otherwise noted, all materials were purchased from commercial suppliers and were used without further purification.

Preparation of 3b.

To a 200 mL flask were added 3,5-dibromoacetophenone (7.92 g, 28.5 mmol)[15] and diethyl ether (60 mL). The flask was cooled at 0 ℃, then triethylamine Et_3N (4.4 mL, 31.7 mmol) and trimethylsilyl trifluoromethanesulfonate TMSOTf (5.7 mL, 31.4 mmol) were added. The mixture was stirred for 20 min, then warmed to room temperature and stirred for 4.5 h. Under air, Et_3N (4 mL) was added, and bottom layer was removed. The solvents were removed under reduced pressure, and then the residue was purified by Kügelrohr distillation (ca. 1 mmHg, oven temp. 165–175 ℃) to give **3b** (9.14 g, 92%) as a clear colorless liquid that was solidified upon cooling. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.64 (d, *J* = 1.6 Hz, 2H), 7.57 (t, *J* = 1.6 Hz, 1H), 4.90 (d, *J* = 2.0 Hz, 1H), 4.48 (d, *J* = 2.0 Hz, 1H), 0.28 (s, 9H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 153.0, 141.1, 133.4, 127.1, 122.7, 92.8, 0.0. EI-HRMS (*m*/*z*): $[M]^+$ calcd for $C_{11}H_{14}OBr_2Si$, 347.9181; found, 347.9182.

Preparation of 3c.

To a 500 mL 4-neck flask were added 3,5-dibromoacetophenone (12.4 g, 44.6 mmol), $PdCl_2(PPh_3)_2$ (1.57 g, 2.23 mmol) and Et_3N (250 mL). The flask was shortly evacuated and refilled with Ar three times, and then trimethylsilylacetylene (19 mL, 134 mmol) and copper iodide (253 mg, 1.33 mmol) were added. The mixture was stirred for 6 h at 65 ℃, then the solvents were removed under reduced pressure. To the residue was added Et_2O, and then the suspension was filtered through a pad of silica gel, eluted with Et_2O. The solvents were removed under reduced pressure. The residue was purified by column chromatography (eluent: hexane/AcOEt = 20/1) to give 6.87 g of 1-(3,5-bis((trimethylsilyl)ethynyl)phenyl)ethan-1-one **S1** as a beige solid. Fractions with insufficient purity were collected and recrystallized from hot methanol to give 5.20 g of **S1** (total yield of **S1**: 12.1 g, 87%). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.95 (d, *J* = 1.6 Hz, 2H), 7.73 (t, *J* = 1.6 Hz, 1H), 2.59 (s, 3H), 0.25 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 196.5, 139.1, 137.1, 131.3, 124.0, 102.9, 96.3, 26.7, –0.2. EI-HRMS (*m*/*z*): $[M]^+$ calcd for $C_{18}H_{24}OSi_2$, 312.1366; found, 312.1359.

To a 100 mL flask were added **S1** (7.82 g, 25.0 mmol) and Et_2O (50 mL). The flask was cooled at 0 ℃, then Et_3N (3.8 mL, 27.5 mmol) was added. To this solution was added TMSOTf (5.0 mL, 27.5 mmol) dropwise over 8 min. The resulting mixture was stirred for 15 min, then warmed to room temperature and stirred further for 2 h. To the biphasic mixture, Et_3N (2 mL) was added, and the bottom layer was removed. After removal of the solvents under reduced pressure, the residue was purified by Kügelrohr distillation (ca. 1 mmHg, oven temp. 206–212 ℃) to give **3c** (5.64 g, 59%) as a clear yellow liquid. ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.61 (d, *J* = 1.6 Hz, 2H), 7.52 (t, *J* = 1.6 Hz, 1H), 4.91 (d, *J* = 2.0 Hz, 1H), 4.46 (d, *J* = 2.0 Hz, 1H), 0.28 (s, 9H), 0.26 (s, 18H). ^{13}C NMR (100 MHz, $CDCl_3$) δ:

154.1, 138.0, 135.0, 128.6, 123.2, 104.1, 94.7, 92.0, 0.1, –0.1. EI-HRMS (*m*/*z*): $[M]^+$ calcd for $C_{21}H_{32}OSi_3$, 384.1761; found, 384.1750.

Electrochemical Generation and Accumulation of Diarylcarbenium Ion 2.

The anodic oxidation was carried out in an H-type divided cell (4G glass filter) equipped with a carbon felt anode (Nippon Carbon JF-20-P7, ca. 320 mg, dried at 250 ℃/1 mmHg for 2.5 h before use) and a platinum plate cathode (20 mm × 10 mm). A solution of **1** (1.55 g, 1.75 mmol) in 0.3 M Bu_4NBF_4/CH_2Cl_2 (35 mL) was placed in the anodic chamber, and a 0.3 M solution of Bu_4NBF_4/CH_2Cl_2 (35 mL) and trifluoromethanesulfonic acid (230 μL, 2.60 mmol) were placed in the cathodic chamber. The constant current electrolysis (40 mA) was carried out at −78 ℃ with magnetic stirring until 2.0 F/mol of electricity was consumed. After the electrolysis, the solution of **2** was transferred by dried glass syringe at −78 ℃ for next polymerization.

General Procedure for Cationic Polymerization of Isobutyl Vinyl Ether Followed by Reaction with Nucleophiles Using a Flow Microreactor System.

After the anodic oxidation of **1**, the solution of **2** (14 mL, −78 ℃) was transferred to a 20 mL flask at −78 ℃. Then 2,6-di-*tert*-butylpyridine (84 mg, 0.44 mmol) was added and the resulting solution was stirred for 10 min at −78 ℃. 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** (inner diameter ϕ = 1000 μm, length L = 50 cm), **P2** (ϕ = 1000 mm, L = 50 cm) and **P3** (ϕ = 1000 mm, L = 50 cm)) was used A solution of isobutyl vinyl ether (0.50 M in CH_2Cl_2, 10 mL/min) and a solution of **2** (5.0 mL/min) containing the proton trapping agent were introduced to **M1**. The mixed solution was passed through **R1** (ϕ = 1000 mm, L = 25 cm) and was introduced to **M2** (ϕ = 500 μm). A solution of **3b** (1.0 M in CH_2Cl_2, 5.0 mL/min) was introduced to **M2** (ϕ = 500 μm), and the resulting solution was passed through **R2** (ϕ = 1000 μm, L = 50 cm). After a steady state was reached, the reaction solution was collected (10 s) and treated with $^{i}Pr_2NH$. The solvent was removed under reduced pressure and the residue was filtered through a silica gel column (2 × 3 cm) using Et_2O as an eluent to remove Bu_4NBF_4. The filtrate was concentrated to obtain a crude product, which was analyzed with size exclusion chromatography (M_n = 5,900, M_w/M_n = 1.06) and purified by preparative GPC to give **4b** (166 mg, 64%). Using **3c** as a terminator, **4c** was obtained using a similar procedure (131 mg, 50%, M_n = 7,100, M_w/M_n = 1.08).

Procedure for Suzuki-Miyaura Cross-coupling Reaction.

To a Schlenk tube were added polymer **4b** (28.9 mg) and dioxane (4 mL), and the Schlenk tube was then shortly evacuated and filled with Ar three times. To the solution were added

$Pd[P(^tBu)_3]_2$ (13 mg, 25 μmol), Cs_2CO_3 (27 mg, 84 μmol), 4-formylphenylboronic acid (11 mg, 75 μmol), and water (40 μL). The mixture was stirred at room temperature overnight, after which was filtered through a plug of silica gel and eluted with EtOAc. The filtrate was evaporated, dried *in vacuo*, and then analyzed with GPC (M_n = 4,600, M_w/M_n = 1.05). Purification with preparative GPC gave **5b** (23 mg, 78%). Using **4a** (M_n = 8,600, M_w/M_n = 1.10, 36 mg) as a starting material, **5a** was obtained using a similar procedure (31 mg, 86%, M_n = 7925, M_w/M_n = 1.19).

Procedure for Scheme 4.

To a Schlenk tube under Ar were added a solution of polymer **4c** (M_n = 7,100, 31 mg) in THF (2 mL), acetic acid (3 μL, 50 μmol) and tetrabutylammonium fluoride (1.0 M in THF, 50 μL, 50 μmol). The mixture was stirred at room temperature for 40 minutes. To this solution were added H_2O (0.5 mL), benzyl azide (3 μL, 25 μmol), sodium ascorbate (10 mg, 50 μmol) and $CuSO_4 \cdot 5H_2O$ (6 mg, 25 μmol), and then the mixture was stirred at 40 ℃ for 2.5 h. H_2O was added, and the mixture was extracted with $CHCl_3$. The extract was dried by passing through a plug of $MgSO_4$, and then evaporated. ^1H NMR analysis showed full conversion of the starting polymer, and appearance of new peaks that can be assigned to **6c**. There was no indication of other by-products. The crude was purified with preparative GPC to give **6c** (31.7 mg, 99%), which was then analyzed with GPC (M_n = 6,600, M_w/M_n = 1.07). To a Schlenk tube was added polymer **6c** (23 mg), and then an atmosphere was replaced to Ar. To the tube were added dioxane (3 mL), $Pd[P(^tBu)_3]_2$ (13 mg, 25 μmol), Cs_2CO_3 (27 mg, 84 μmol), 4-formylphenylboronic acid (11 mg, 75 μmol), and H_2O (30 μL). The mixture was stirred at 30 ℃ for 3.5 h, then filtered through a plug of silica gel and eluted with $CHCl_3$. The filtrate was evaporated, dried *in vacuo*, and then purified with preparative GPC to give **7c** (19.7 mg, 85%), which was then analyzed with GPC (M_n = 7,300, M_w/M_n = 1.07).

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